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# The use of the corpus cavernosum for the administration of phenobarbital: an experimental study in dogs

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**Abstract**

Status epilepticus (SE) is classically defined as a generalized tonic-clonic seizure lasting longer than 30 min. Prolonged seizure activity can be resulted in irreversible cerebral injury. In addition, the existence evidence suggests that the longer the duration of the seizure activity is less likely to be controlled. The intravenous (IV) access is frequently difficult during SE, especially in infants and neonates. On the other hand, it has been demonstrated that high volumes of fluid can be injected into the corpora cavernosa. In this study, phenobarbital (PB) was administered to dogs using both IV and intracavernous (IC) routes with a dose of 20 mg/kg. The time period required to establish the IC route was less than 5 s. The levels of PB in the blood were measured and all results were compared. There was no statistically significant difference between the IV and IC administration with regard of the blood PB levels. Within 48 h of the experiment, none of animals demonstrated any evidence of infection or disability. Our findings suggest that the IC route may be an alternative route for the administration of PB when venous access is not immediately available or if it is not possible to achieve. 

*Keywords:* Phenobarbital; Status epilepticus; Intravascular access; Intracavernous route

## 1. Introduction

Status epilepticus (SE) is classically defined as a generalized tonic-clonic seizure if it is prolonged for more than 30 min. Some investigators have suggested that a better definition would be included if the seizure persists for more than twice

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than its normal duration (Ramsay, 1993). Prolonged seizure activity can result in irreversible cerebral injury as a result of excessive metabolic demands and depletion of nutrients (Lothman, 1990). Furthermore, the existence evidence suggests that the longer the duration of the seizure activity the less likely it is to be controlled (Walton and Treiman, 1991). Initial management of SE includes the ABCs of life support (supporting respiration, maintaining blood pressure, gaining access to circulation etc. and when it is possible, identifying and treating the possible cause). However, administering an antiepileptic drug is a top priority because managing to keep the airway open and assisting the respiration are much easier after the convulsion is stopped. Therefore, clinical and electrical seizure must be terminated rapidly.

Intravenous (IV) phenobarbital (PB) has been used for years to treat SE, especially in newborns, infants, and children (America's working group on status epilepticus, 1993). No difference was found in one comparison of PB to diazepam plus phenytoin in convulsive SE (Shanner et al., 1988). High enough doses can control almost all seizures. Very high doses require artificial ventilation and may cause hypotension, but this may be tolerated better than expected (Crawford et al., 1988).

Rapid IV access for the administration of anticonvulsants in seizing patients can be one of the most difficult and time-consuming procedures that a physician frequently faces. It has been reported that peripheral IV access was achieved in only 21% of children who presented with seizures (Kendall et al., 1997). In addition, attempts for IV injection during SE can pose risks to the patient and caregivers. For these reasons, an alternative route of delivering medication to the patient during SE is desirable.

It has been suggested that intracavernous (IC) route for fluid administration is a vital emergency alternative for the venous access for males (Godec and Cass, 1982). To our knowledge, there is no study available on the investigation of IC administration of PB. The purpose of this study was to evaluate whether therapeutic serum levels of PB can be obtained by the IC route or not.

## 2. Material and methods

Ten adult dogs weighing 8.7–9.8 kg were determined to be normal by physical examination. They were anesthetized with ketamine with a dosage of 1 mg/kg (IV). Animals were assigned into two groups (5 dogs for each): IC and IV. They underwent a surgical procedure for the 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 PB. Both catheters were secured at their entry site with nylon sutures. In the IV group, PB (20 mg/kg of body weight) was administered into the catheter in the right femoral vein over 5 min. In the IC group, a 26 gauge needle was inserted into one of the corpora cavernosa of the mid shaft of the penis, directed obliquely at an angle of 30° towards to the radix of the penis. PB was diluted with normal saline to a 1:1 ratio and injected directly into the corpus cavernosum (the same dose as administered to the IV group) over 5 min. Subsequent to the injections, the needles were flushed with 1 ml of normal saline. After the IC administrations were completed, pressure was applied to the injection site on the corpus cavernosum to prevent hematoma. Antibiotic ointment was then placed on the injection site. Plasma samples were drawn from the right femoral vein into glass tubes following PB administration. Animals were observed until the effects of sedation had cleared out. An appropriate institutional review board approved the project, and all animals were treated in a humane fashion and recovered with adequate pain control after the procedure.

### 2.1. Analysis of phenobarbital in blood samples

Blood was collected in vacutainer tubes (Belliver Industrial Estate, Plymouth PL6 7BP, UK). Plasma was separated and frozen immediately at −20 °C until analyzed. PB contents of the plasma were determined using a fluorescence polarization immunoassay (FBIA; TDx, Abbott Diagnostics, North Chicago, IL). Plasma samples containing only unbound fractions of PB were prepared by ultrafiltration using the Centrifree Micropartition System (no. 4104; Amicon, Danvers, MA). Approximately 1 ml of plasma was pipetted into the

ultrafiltration device, then centrifuged at 1500 × *g* at 25±2 °C for 20 min. The within-run coefficients of variation for the analysis procedures of PB were < 5.0%.

## 3. Results

Five dogs (IC group) received an IC injection. Insertions of the needle using this method were successful in all cases. The time required to establish this procedure was less than 5 sec. In the other 5 dogs (IV group), the same dose of PB was administered intravenously for the same duration through the catheter in the right femoral vein. The PB content of the plasma samples were analyzed and blood profiles were determined. Mean PB levels in blood are shown in Fig. 1 comparing IV and IC administration. The data for each of the respective groups were statistically compared using analysis of variance. The blood profile in the IC group increased rapidly after administration ($t_{max} \cong 20$ min, $C_{max} \cong 25$ μg/ml) and it was found to be comparable with the IV level after few minutes. Although blood levels of PB after IC administration were found to be lower than IV level at the beginning, the differences between the two groups were not significant at any point ($P > 0.05$). AUC values and biological half lifes were also calculated ($AUC_{IV} = 697.51 \pm 304.29$ μg/ml min, $AUC_{IC} = 996.94 \pm 321.12$ μg/ml min; $t_{1/2\ IV} = 19.87 \pm 6.30$ min, $t_{1/2\ IC} = 17.81 \pm 10.50$ min) and differences were again not found to be statistically significant.

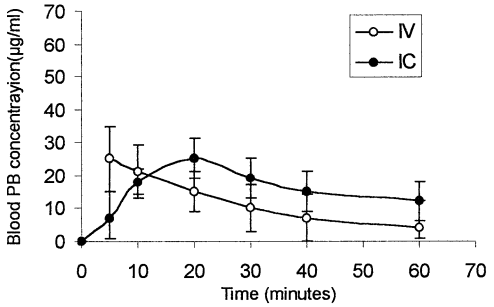


Fig. 1. The blood PB levels in dogs following the IV and IC administration.

The dogs were followed-up for a period of 48 h and no local or systemic complications from these applications were observed in this study.

## 4. Discussion

PB does not enter the brain as rapidly as lipophilic drugs, such as the benzodiazepines; however, the therapeutic brain level is reached in 3 min and is maintained for hours (Ramsey et al., 1979). There is evidence that cerebral uptake is enhanced by seizure activity (Walton and Treiman, 1989). PB can be given intravenously, intramuscularly, and orally. During SE, IV form should be administered to the patients, as the oral administration is not possible and absorbed lately. IM administration of PB also takes approximately 45 min to act (Pearce et al., 1977; Payne and Bleck, 1997).

Intraosseous infusion has been shown to be a rapid and effective alternative to IV access for the administration of PB (Brickman et al., 1987; Jaimovich et al., 1989; Garettson and McGee, 1992). But, to be an effective mode of therapy, it is critical to achieve a single-attempt intraosseous needle placement for intraosseous infusion; it has been demonstrated that there is a significant difference in serum PB levels during a 10-min period between the single- and multiple-attempt intraosseous infusions, and it has been suggested that multiple attempts lead to a significant extravasation into the surrounding soft tissues during the infusion and, thus, deliver much less of the infused medication from the intramedullary spaces to the vascular system (Brickman et al., 1990). Moreover, some complications like an infection, fat emboli, fracture, compartment syndrome, etc. were attributed to this procedure (La Fleche et al., 1989; Moscati and Moore, 1990; Vidal et al., 1993; Orlowski, 1994).

There is a general need to achieve an effective route for delivering an anticonvulsant drug during the seizure which is not effected by uncontrollable seizure movements and spasms. Godec and Cass (1982) have first suggested that high volumes of fluid can be injected into the corpora cavernosa. There has been another study reporting that the

mean rate of saline infusion into the corpus cavernosum was $50.2 \pm 0.7$ ml/min in severely hypovolemic dogs (Stein and Gray, 1995) In an other investigation, it has been shown that the mean infusion rate through the canine corpora was $110 \pm 22$ ml/min for Ringer's lactate solution and $109 \pm 18$ ml/min for autologous blood. The mean infusion rate into the human corpora was $89.7 \pm 12$ ml/min in the psycogenic impotent patients, and $88.2 \pm 9$ ml/min in the organic impotent patients (Gofrit et al., 1997). The IC route is not just for volume infusions. It should be considered whenever a life-threatening illness requires immediate drug therapy; it has been reported that blood is diverted from the corpora cavernosa directly into the venous system when the penis is flaccid (Meuleman and Diemont, 1995). It is likely that the drugs leak into the venous circulation by IC injection and cause systemic effects. But, until now, as far as we know, this maneuver has never been investigated for the administration of PB. PB administration by IC was achieved in this study. This route cannot be affected by uncontrollable seizure movements and spasms during the SE.

For full effectiveness, with a dose of 20 mg/kg and a rate of 100 mg/min recommended, even though control is frequently achieved with much smaller doses (Shanner et al., 1988). The same dose was used in both groups in the present study. The mean time to insert the needles was less than 5 sec in the IC group. The blood profile in the IC group increased rapidly after the administration and it was found to be comparable with the IV level after few minutes. The differences between the two groups were not statistically significant at any point ($P > 0.05$). Our preliminary results showed that PB can be absorbed by the IC route in dogs.

The levels of PB at the beginning in the IC group were slightly less than those of the IV group, even though this difference was not significant (Fig. 1). This may be explained by retention of PB in the corpus cavernosum after injection. The canine corpora is composed of two completely separate systems. In contrast to the canine corpora, there are multiple vascular communications between the two corpora cavernosa of human penis which make possible to fill both corpora with a single needle. Therefore, it may be possible to reach IV blood level by using the IC route. Moreover, it may be possible to obtain similar blood levels as with a IV administration using higher dose of PB or larger volume of the diluent if it is necessary.

Although PB in the currently available commercial form was well absorbed when administered intracavernously, its possible adverse effects on the cavernous tissue remains unclear. Even though some local irritation might occur, it may be acceptable, but a new formulations may be developed which contain non-toxic excipients. Certainly this needs further investigations.

## References

Brickman, K., Rega, P., Choo, M., Guinness, M., 1990. Comparison of serum phenobarbital levels after single versus multiple attempts at intraosseous infusion. Ann. Emerg. Med. 19, 31–33.

Brickman, K.R., Rega, P., Guinness, M., 1987. A comparative study of intraosseous versus peripheral intravenous infusion of diazepam and phenobarbital in dogs. Ann. Emerg. Med. 16, 1141–1144.

Crawford, T.P., Mitchell, W.G., Fishman, L.S., Snodgrass, S.R., 1988. Very-high dose phenobarbital for refractory status epilepticus. Neurology 38, 1035–1040.

Garettson, L.K., McGee, E.B., 1992. Rapid onset of seizures following aspiration of viscous lidocaine. J. Toxicol. Clin. Toxicol. 30, 413–422.

Godec, C.J., Cass, A.S., 1982. The penis—a possible alternative emergency venous access for males? Ann. Emerg. Med. 11, 266–268.

Gofrit, O.N., Leibovici, D., Shapira, S.C., Michaelson, M., Shofti, R., Mordochovich, D., Vardi, Y., 1997. Penile intracorperal infusion—possible access to the systemic circulation. Pressure flow studies in dogs and humans. Eur. J. Surg. 163, 457–461.

Jaimovich, D.G., Shabino, C.L., Ringer, T.V., Peters, G.R., 1989. Comparison of intraosseous and intravenous routes of anticonvulsant administration in a porcine model. Ann. Emerg. Med. 18, 842–846.

Kendall, J.L., Reynolds, M., Goldberg, R., 1997. Intranasal Midezolam in patients with status epilepticus. Ann. Emerg. Med. 29, 415–417.

La Fleche, F.R., Slepin, M.J., Vargas, J., Milzman, D.P., 1989. Iatrogenic bilateral tibial fractures after intraosseous infusion attempts in a 3-month-old infant. Ann. Emerg. Med. 18, 1099–1101.

Lothman, E., 1990. The biochemical basis and pathophysiology of status epilepticus. Neurology 40, 13–23.

Meuleman, E.J., Diemont, W.L., 1995. Investigation of erectile function. Diagnostic testing for vascular factors in erectile dysfunction. Urol. Clin. North Am. 22, 803–819.

Moscati, R., Moore, G.P., 1990. Compartment syndrome with resultant amputation following intraosseous infusion. Am. J. Emerg. Med. 8, 470–471.

Orlowski, J.P., 1994. Emergency alternatives to intravenous access. Intraosseous, intratracheal, sublingual, and other-site drug administration. Pediatr. Clin. North Am. 41, 1183–1199.

Payne, T.A., Bleck, T.P., 1997. Status epilepticus. Crit. Care Clin. 13, 17–38.

Pearce, J.L., Sharman, J.R., Forster, R.M., 1977. Phenobarbital in the acute management of febrile convulsions. Pediatrics 60, 569–572.

Ramsay, R.E., 1993. Treatment of status epilepticus. Epilepsia 34, S71–81.

Ramsey, R.E., Hammond, E.J., Perchalsli, R.J., Wilder, B.J., 1979. Brain uptake of pnenytoin, phenobarbital, and diazem. Arch. Neurol. 36, 535–539.

Recommendations of the epilepsy foundation of America's working group on status epilepticus, 1993. Treatment of convulsive status epilepticus. JAMA, 270, 854–859.

Shanner, D.M., McCurdy, S.A., Herring, M.O., Gabor, A.J., 1988. Treatment of status epilepticus: a prospective comparison of diazepam and phenitoin versus phenobarbital and optional phenytoin. Neurology 38, 202–207.

Stein, M., Gray, R., 1995. Corpus cavernosum as an emergency vascular access in dogs. Acad. Radiol. 2, 1073–1077.

Vidal, R., Kissoon, N., Gayle, M., 1993. Compartment syndrome following intraosseous infusion. Pediatrics 91, 1201–1202.

Walton, N.Y., Treiman, D.M., 1989. Phenobarbital treatment of status epilepticus in a rodent model. Epilepsy Res. 4, 216–221.

Walton, N.Y., Treiman, D.M., 1991. Motor and electroencephalographic response of refractory experimental status epilepticus in rats to treatment with MK-801, diazepam, or MK-801 plus diazepam. Brain Res. 553, 97–104.