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THE LOADING OF PHENYTOIN BY THE INTRAPENIL ROUTE
An experimental study in rabbits

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ABSTRACT: Rapid venous access may be a challenge during emergency, especially in pediatric cases. On the other hand, it has been suggested that high volumes of fluid can be injected into the corpora cavernosa. One of the emergency situations required rapid intravenous (IV) access is status epilepticus (SE). Phenytoin (PHT) is one of the major drugs used in the treatment of SE. As far as we know, there has no investigation comparing IV and intracavernous (IC) loading of PHT. In this study, PHT was administered to rabbits using both IV and IC routes at the dose of 20 mg/kg. Saphenous vein blood samples were drawn at 1, 5, 10, 15, 20, 25, 30 minutes following administration in both the IC group and the IV groups. Serum PHT concentrations were determined and their profiles were compared. Although the blood levels of PHT were found to be statistically significantly lower with IC administration, but it was found to be higher than minimum effective concentration. Our study showed that PTH can be absorbed by the IC route as fast as by the IV route. Research is needed to study this technique in more detail before clinical applications.
[Key Words: Phenytoin, status epilepticus, intravascular access, intracavernous route]

INTRODUCTION

Rapid venous access can be a challenge during emergency, especially in small children. It has been reported that IV catheterization was completed within five minutes in only 66%, required more than 10 minutes in 24%, and could not be established in 6% of children in emergency situation. Venous cut down time averaged 24 minutes in these children (1-2). One of the emergency situations require rapid IV access is status epilepticus (SE). SE has been defined as a 'condition characterized by an epileptic seizure that is sufficiently prolonged or repeated so as to produce a fixed and lasting epileptic condition' (3). Prolonged seizure activity can result in irreversible cerebral injury as a result of excessive metabolic demands and nutrient depletion (4). Furthermore, evidence suggests that the longer the duration of the seizure activity the less likely the activity is to be controlled (5). Clinical and electrical seizure must be terminated rapidly. IV access, however, is frequently difficult to achieve during SE. It has been reported that peripheral IV access was achieved in only 21% of children who presented with seizures (6). In addition, attempts at IV 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 SE is desirable. It has been suggested that intrapenil route of fluid administration is a viable emergency alternative for venous access in the male (7).

Phenytoin (PHT) is one of the major antiepileptic drugs used frequently, especially in infants and neonates. To our knowledge, there is no study on the intracavernous (IC) administration of PHT. The purpose of this study was to investigate the IC route as a mode of administrating PHT by examining the serum levels.

MATERIALS AND METHODS

Materials: PHT and ketamine were obtained from Eczacıbaşı Warner Lambert Drug Company (Eczacıbaşı Drug Co., Büyükdere street, No: 185, Levent, 80710, İstanbul, Turkey). Other chemicals and reagents were of analytical grade

Methods: Ten New Zealand White adult rabbits (mean weight, 2.75 kg; range 2.50 to 2.90 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. After adequate anesthesia was obtained, saphenous vein was cannulated for obtaining blood PHT levels. This was kept open by means of a heparin lock. Animals were assigned to two groups of five rabbits. In first group (IV group), PHT (20 mg/kg of body weight) was diluted in 1 cc normal saline and administered into the exterior ear vein over 30 seconds. In second group (IC group), 26 gauge needle inserted into the corpus cavernosum of the mid shaft of the penis, directed at an angle of 30 ˚ toward to the radix of the penis. PHT at the same dose without dilution was injected directly into the corpus cavernosum, over 1 minute. After administrations were completed, pressure was applied to the injection site to prevent hematoma formation. Antibiotic ointment was then placed on the entry site.

Blood samples were collected from the saphenous vein of each rabbit into tubes at 1, 5, 10, 15, 20, 25, 30 minutes following PHT administration. Animals were observed until the effects of sedation had cleared. An appropriate institutional review board approved the project.

Determination of serum PHT 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 PHT were < 5.0%.

Statistic: Statistical analysis was performed using a computer program called Graphpad Instat version 2.04a. alternate t-test was used for the comparison which assumes Gaussian populations with different standard deviations. The two-tailed p values were calculated and used to understand significant differences.

RESULTS

The IC injection procedures were applied in five rabbits (the IC group). Insertions of the needle using this method were successful in all cases. The time required to establish this procedure was less than 5 seconds. IV group (the other five rabbits) received the same dose of PHT intravenously through the exterior ear vein. The PHT contents of the serum samples were analyzed and blood profiles were determined. Mean PHT levels in µg/ml are shown (Table-1) at 1, 5, 10, 15, 20, 25, 30 minutes following administration in both the IC group and the IV groups. Mean serum PHT levels are shown also graphically (Figure-1). PHT levels in IV group were as expected, decreasing exponentially at each respective interval. In IC group, blood PHT levels were found to be comparable with the IV

Table 1. Blood PHT concentrations after IV and IC administrations in rabbits.

Time (minutes)	IC ± SD (n=5)	IV ± SD(n=5)	P value
1	20.567±5.727	53.799±8.164	p<0.0001
5	17.767±5.835	46.597±8.352	0.0004
10	16.059±5.135	38.824±8.026	0.0018
15	15.765±5.554	34.849±4.518	0.0006
20	15.597±4.389	31.945±5.695	0.0014
25	17.011±5.450	28.762±5.184	0.0088
30	18.621±3.442	26.401±6.403	0.0538

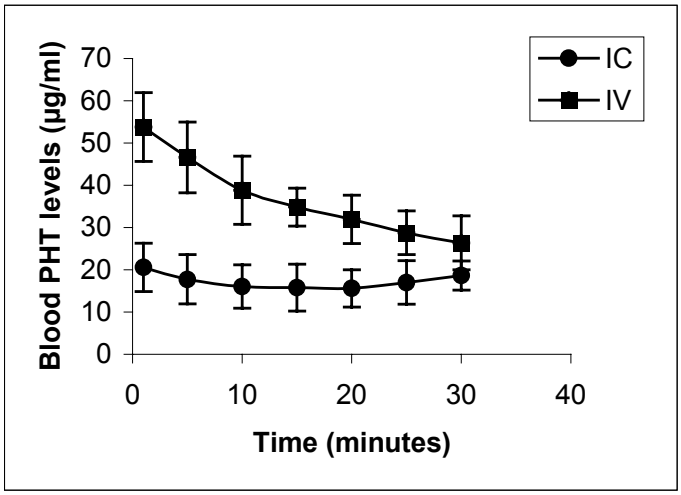

Figure 1. Serum PHT concentrations after IV and IC administrations in rabbits (Error bars represent SEM, n=5).

administration considering the effective PHT blood level. The data for each of the respective groups were statistically compared. Thus when blood PHT levels for each group were subjected to statistical analysis, the differences were found to be statistically significant. Although the blood level of PHT after IC administration was found to be lower than IV level at each interval, all the values were higher than minimum effective concentration.

Within 48 hours after investigation, none of animals demonstrated any evidence of infection or disability.

DISCUSSION

PHT is one of the antiepileptic drugs used frequently. In the absence of acute structural lesions, it may be the only necessary antiepileptic drug in as much as 80% of the patients who have generalized convulsive SE. Moreover, it may have a benefit before reaching therapeutic levels (8-9). As PHT is slowly absorbed rectally, it is not recommended to be given during SE. PHT is not highly soluble in water especially in acidic medium because of its pKa. As the muscle environment is more acidic than blood, the

sodium salt of PHT can easily be precipitated at the site of injection. This is resulted in slow and erratic absorption from intramuscular injection sites. Therefore, it has been recommended to be administered only intravenously (10-12).

As rapid IV access for the administration of PHT during seizure activities may be very difficult and time-consuming procedure, alternative ways have been investigated; intraosseous infusion has been shown to be a rapid and effective alternative to intravenous access for the administration of PHT (13-15). But, in another similar study, it has been shown that intraosseous administration of 15 mg/kg dose of PHT does not maintain therapeutic levels, and intraosseous infusion is not recommended for the PHT loading (16). Moreover, some complications like infection, fat emboli, fracture, compartment syndrome, etc. were attributed to this procedure (17-20).

There is a general need to achieve an effective route for delivering an anticonvulsant drug which is not effected by uncontrollable seizure movements and spasms. CJ Godec and AS Cass have first suggested that high volumes of fluid can be injected into the corpora cavernosa(7). Then, there has been an other study reported that the mean rate of saline infusion into the corpus cavernosum was 50.2 ± 0.7 ml/min. in severely hypovolemic dogs (21). In an other investigation, it has been shown that the mean infusion rate through the canine corpora was 110 ± 22 ml/ minute for Ringer's lactate solution and 109 ± 18 ml/minute for autologous blood. The mean infusion rate into the human corpora was 89.7 ± 12 ml/min. in the psycogenic impotent patients, and 88.2 ± 9 ml/minute in the organic impotent patients (22). 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 (23). 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 concern, this maneuver has never been investigated for the administration of PHT. We think that IC route may be very suitable for the drug administration during the seizure activities and it was tested for PHT administration in this study. It has been earlier shown that the effects of vasoactive drugs on the rabbit's corpus cavernosum are similar to those in humans, and suggested that the rabbit model is a suitable alternative for physiological and pharmacological studies of penile erection (24). Therefore the rabbit model was preferred in this study also.

The usual PHT dose is 10 to 20 mg/kg. In the present study, 20 mg/kg dose was selected and applied to make a better comparison. Although the rate of IV infusion should not exceed 50 mg/minute in adult and 1 mg/kg/min in children, the perfusion time was selected rather short (30 seconds for IV, a minute for IC administration) to understand the effect and difference of the application methods. PHT was used as a solution in commercial product form and was not diluted further for IC application because of the limited volume of the cavernous tissue. All the attempts for the insertions of the needle using this method were successful, and the time for inserting the needles was less than 5 seconds in all rabbits. Considering the organ sizes, it may be easier to manipulate in humans.

Our preliminary results showed that commercially available parenteral PHT can be absorbed when given undiluted and unmodified by the IC route in rabbits. The plasma levels of PHT at the all intervals in the IC group were significantly less than those of the IV group, this may be explained by retention of PHT in the corpus cavernosum after injection. Considering the organs sizes, it may be possible to achieve higher plasma levels by administering the PHT through IC route in humans. Moreover, it is possible to inject the larger volume by the use of much more diluents or alteration in drug dosage may be

useful to increase the absorption. On the other hand, the fact that slower rise in blood PHT levels observed, comparing with IV delivery may be the important safety factor as it has been reported that IV administration of PHT can produce some cardiovascular adverse effects like atrial and ventricular conduction depression, ventricular fibrillation or hypotension which are usually related to the rate of infusion (9-25).

Although PHT in the currently available commercial form was well absorbed when administered via the IC route, its possible adverse effects on the cavernous tissue that may preclude the IC use remained unclear. Both the PHT and the vehicle used in these preparations may have adverse effects on the cavernous tissue because of high pH; it has been reported that there is a risk for thrombophlebitis at the site of injection or frank tissue necrosis if the drug extravasates out of the vein into surrounding tissue [10]. On the other hand, it has been shown that intraosseous infusion of PHT has no permanent damage by the microscopic examination of the cortex and marrow at the intraosseous site after 5 weeks of infusion in pigs (15). There is no study about the effects of PHT on cavernous tissue. Large-scale experimental studies are needed to investigate the acute and chronic local toxic effect of this application. If such irritation is shown, it may be acceptable or the new formulations, which contain good non-toxic excipients, may be developed in the future investigations.

CONCLUSION

Our results suggest that IC injection may be an efficient alternative way for the loading of PHT when IV lines cannot be quickly established in patients in SE. Further studies are needed to establish the clinical utility of this application. If these results are confirmed, and possible irritation potentials are overcome, the use of IC injection of PHT may be used for the management of SE as this method is easy and quick to do after minimal training (impotent patients are able to use IC route for auto injections) and no special equipment is needed. Although İC route effectivenes, there is not enough pediatric clinical experiences and further clinical studies needed.

REFERENCES

1. Rosetti V, Thompson BM, Aprahamian C, et al. Difficulty and delay in intravascular access in pediatric arrests. Ann Emerg Med, 13: 406, 1984.
2. Kanter RK, Zimmerman JJ, Strauss RH, Stoeckel KA. Pediatric emergency intravenous access. Am. J. Dis. Child, 140: 132-134, 1986.
3. Gaustaut H. Clinical and electrographic classification of epileptic seizures. Epilepsia, 11: 102-113, 1970.
4. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology, 40 (suppl 2): 13-23, 1990.
5. Walton NY, Trieman DM. Motor and electroencephalographic response of refractory experimental status epilepticus to treatment with mk-801, diazepam, or mk-801 plus diazepam. Brain Res, 553: 97-104, 1991.
6. Kendall JL, Reynolds M, Goldberg R. Intranasal Midezolam in patients with status epilepticus. Ann Emerg Med, 29: 415-417, 1997.
7. Godec CJ, Cass AS. The penis-a possible alternative emergency venous access for males? Ann Emerg Med, 11: 1266-268, 1982.
8. Cranford RE, Leppik IE, Patrick B et al. Intravenous phenytoin in acute treatment of seizures. Neurology, 29: 1474-1479, 1979.
9. Roth HL, Drislane FW. Seizures. Neurol Clin, 16: 257-284, 1998.
10. Payne TA, Bleck TP. Status epilepticus. Crit Care Clin, 13: 17-38, 1997.

11. Bone RC. Concepts in emergency and Critical care, Working group on status epilepticus. Treatment of convulsive status epilepticus. JAMA, 270: 854-859, 1993.
12. Loebstein R, Koren G. Clinical pharmacology and therapeutic drug monitoring in neonates and children. Pediatr Rev, 19: 423-428, 1998.
13. Walsh-Kelly CM, Berens RJ, Glaeser PW, Losek JD. Intraosseous infusion of phenytoin. Am J Emerg Med, 4: 523-524, 1986.
14. Smith RJ, Keseg DP, Manley LK et al. Intraosseous infusions by prehospital personnel in critically ill pediatric patients. Am J Emerg Med, 17: 491-495, 1988.
15. Vinsel PJ, Moore GP, O'Hair KC. Comparison of intraosseous versus intravenous loading of phenytoin in pigs and effect on bone marrow. Ann Emerg Med, 8: 181-183, 1990.
16. Jaimovich DG, Shabino CL, Ringer TV et al. Comparison of intraosseous and intravenous routes of anticonvulsant administration in a porcine model. Ann Emerg Med, 18: 842-846, 1989.
17. Orlowski JP. Emergency alternatives to intravenous access. Pediatr Clin North Am, 41: 1183-1199, 1994.
18. Moscati R, Moore GP. Compartment syndrome with resultant amputation following intraosseous infusion. Am J Emerg Med, 8: 470-471, 1990.
19. La Fleche FR, Slepin MJ, Vargas J et al. Iatrogenic bilateral tibial fractures after intraosseous infusion attempts in a 3-month-old infant. Ann Emerg Med, 18: 1099-1101, 1989.
20. Vidal R, Kissoon N, Gayle M. Compartment syndrome following intraosseous infusion. Pediatrics, 91: 1201-1202, 1993.
21. Stein M, Gray R. Corpus cavernosum as an emergency vascular access in dogs. Acad Radiol, 2: 1073-1077, 1995.
22. Gofrit ON, Leibovici D, Shapira SC, et al. Penile intracorperal infusion-possible access to the systemic circulation. Pressure flow studies in dogs and humans. Eur J Surg 163: 457-461, 1997.
23. Meuleman EJ, Diemont WL. Investigation of erectile function. Urol. Clin North Am 22: 803-819, 1995.
24. Lin YM, Lin JS. The rabbit as an intracavernous injection study model. Urol Res 24: 27-32, 1996.
25. Mattson RH. Parenteral antiepileptic / anticonvulsant drugs. Neurology, 46:-13, 1996.

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