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INTRAOSSEOUS INFUSION OF DIAZEPAM USING SPINAL NEEDLE

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ABSTARCT: Seizure can cause serious brain damage if it prolongs. It is general need to terminate seizure as soon as possible using anticonvulsant drugs via intravenous (IV) route. But, it is very difficult to achieve secure IV line during the seizure. On the other hand, intraosseous (IO) access is available. In this study, diazepam was administered to rabbits using both IV and IO lines at the dose of 0.2 mg/kg. Blood samples were collected from ear vein for time period of 20 minutes and analyzed. Blood plasma diazepam concentrations were determined and their profiles were compared. The IO line appeared to be an alternative route to IV access in the administration of diazepam.
[Keywords: Diazepam, bone marrow infusion, intraosseous infusion, spinal needle, intravascular access]

INTRODUCTION

Seizure is a common pediatric problem and represents the most frequent non-traumatic pre-hospital complaint in patients less than 18 years old. An individual's lifetime risk of having a seizure is approximately 10%. Epilepsy will occur in 3-4% of the population at some point (0.5-1.0 at any given time), 3-4% will have acute reactive seizures, 1% will have a single unprovoked seizure, and 2% will have febrile seizures before age 5. Seizures account for almost 1% of emergency room visits, and they prompt more concern and investigation about the seizure than many other conditions (1-5). Initial assessment is similar to all emergency cases, with attention directed first toward airway, breathing, and circulation (ABC's). Clinical and electrical seizure must be terminated rapidly. Diazepam is generally accepted as a drug of choice for the treatment of seizure; IV diazepam administration results in termination of SE in approximately 80% of cases (6).

Despite improvements in technique and equipment for obtaining venous access, it is not always possible to achieve a secure peripheral or central IV line as expeditiously as desired. This is especially difficult for fat pediatric patients, the small vasculature, the anatomical variation from adults. It has been reported that peripheral IV access was achieved in only 21% of the children who presented seizure (7). In addition, attempts at both IV and IM injections during seizures can pose risks to the patient and caregivers. For these reasons, an alternative route for delivering medication to the patient in seizure is desirable. IO infusion is a potential alternative route for intravenous access (8).

The purpose of this study was to determine the plasma level of diazepam if it is absorbed after IO administration and to understand whether it is therapeutically significant or not.

MATERIALS AND METHODS

Materials

Diazepam obtained from Deva Drug Company (Barbaros street, Ak İŞ Hanı, No:64, Zincnirli kuyu, İstunbul, Turkey), Ketamine (Eczacıbaşı Drug Co., Büyükdere street, No:185, Levent, 80710, İstanbul, Turkey) was purchased from the market. Other chemicals and reagents were of analytical grade.

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. Animals were divided in two groups.

In first group, after adequate anesthesia was obtained, a 22-gauge spinal needle (UNIEVER, UNISIS CORP., Tokyo, JAPAN) was introduced in the medial aspect of the proximal tibia, directed at an angle of 30° away from the physis. A screwing motion was used until needle reached to the marrow, which was noted by decreasing resistance. The intramedullary placement was confirmed by return of marrow elements. Diazepam was diluted with normal saline to a 1:1 ratio and infused over 5 minutes. Subsequent to the infusion, the needles were flushed with 5 mL normal saline. Total dose was 0.2 mg/kg. A 24-gauge peripheral intravenous catheter was inserted in an ear vein. Venous blood samples were collected by time. After administrations were completed, the IO 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. In second group (control group), diazepam at the same dose was administered by IV route to the rabbits over 5 minutes. Subsequent to the injection, the needles were flushed with 5 mL normal saline. Blood samples were collected by the time from the vein as mentioned above and analyzed. The results were compared.

Analysis of diazepam in plasma:

Diazepam was analyzed by HPLC (High Pressure Liquid Chromatography). Hewlett Packard (model 1050) was used. 1.5 to 2 ml of blood samples were taken and centrifuged. 0.5 ml of plasma was taken and 200 μl of potassium carbonate (2.5 M) was added and this mixture was extracted with 3 ml of diethyl ether for a minute using vortex mixer. 2 ml of organic phase was taken and 100μl of H_2SO_4 (0.05 M) was added and vortexed for minute. Aqueous phase was taken and injected to the HPLC. An HPLC method was developed. A C_{18} column was used. Mobile phase was consisted of methanol:acetonitrile:water containing 0,02M KH_2PO_4 (17:15:68). Flow rate was 0.8 ml/min., injection volume was 50 μl. Diazepam was detected at 254 nm. and retention time was about 13 minutes. Calibration curve was obtained using peak areas (r^2=0.998). Detection limit was 0.1 µg/ml.

RESULTS

The diazepam contents of the plasma samples were analyzed and blood profiles were determined after IV and IO diazepam administration. Figure 1 shows the blood profiles. Within 48 hours after investigation, all animals were able to move easily and they could use the drug administered legs without any difficulty. None of animals demonstrated any evidence of infection or disability after investigation.

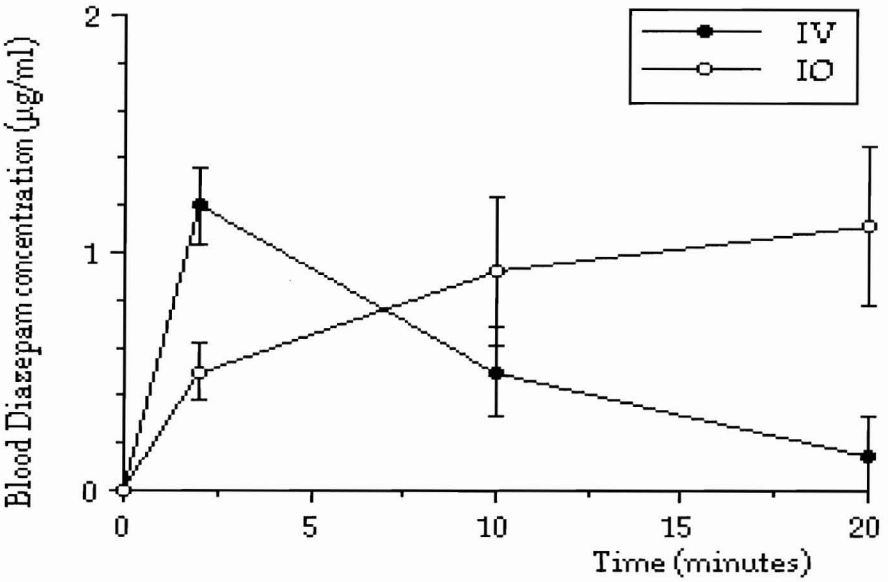

Figure.1: Blood diazepam concentrations after IV and IO administrations (Error bars represent SEM, n=5).

DISCUSSION

Diazepam is not recommended for IM injection because of soft-tissue irritation and reported delay action nearly 60 minutes before therapeutic peak level achieved. Rectal diazepam is absorbed erratically. The endotracheal administration of diazepam has gained much disfavor because of concern of alveolar integrity (9,10,11).

IO infusion is a technique for the administration of fluids and drugs to a child who is in a state of hemodynamic collapse or in whom attempts to access the vascular system by conventional means have not been successful. Bone marrow needles, lumbar puncture needles and specially designed IO canulae have been used for this purpose. This method is used most efficiently in children from three months to three years old because of the presence of highly vascular marrow and large venous sinusoids in the long bones.

The IO and IV diazepam administration results has been compared in the literature, in controlling pentylenetetrazol-induced epileptogenic activity in pigs, it has been found that there was no time difference to abolish seizure activity or difference in diazepam levels (12).

Multiple IO sites previously suggested included the proximal tibia, medial malleolus, distal femur, proximal humerus, iliac crests, and sternum. The proximal tibia is most widely used because it provides an easily identifiable and accessible location. In the present study also, this site is preferred as performed clinically.

The literature notes several potential complications with the use of IO infusion. Osteomyelitis has been reported in less than 1% of cases. It is more probable if hypertonic solutions have been injected or infusion is prolonged beyond the emergency situations. Multiple IO administration attempts in one bone will cause drugs and fluids to leak through the holes when infusion is attempted through that particular bone. Local extravasation of fluids can occur producing a compartment syndrome with resultant limb

amputation. There are also case reports of the needle producing fractures of the tibial bone in attempts at IO infusion (13,14,15). All these complications have been generally attributed to the poor operator technique, the duration of the needle in situ and the infusion of hypertonic solutions (8,16,17). It is possible to avoid them by using the recommended techniques and management.

In the present study, There was not any complication observed, since needle insertion was done by experienced personnel and under controlled conditions.

We suggest that IO infusion is an efficient way to establish emergency vascular access for the administration of diazepam when intravenous lines cannot be quickly established in patients in seizure.

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