Administration of Anticonvulsant Drugs by the Intraperitoneal Route

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Abstract

Status epilepticus or seizures cause serious brain damages and irreversible cerebral injury if it prolongs and it is essential to terminate seizure rapidly. Antiepileptic drugs can be introduced to the patients intravenously (IV), but it is almost impossible to achieve IV access during the seizure. Intraperitoneal (IP) route can be accessible but, IP route of administration of antiepileptic drugs has not been used so far. Therefore the possibility of IP administration of antiepileptic drugs was investigated in this study. Antiepileptic drug (diazepam, phenytoin or phenobarbital) was introduced rabbits and dogs by IV and IP routes and blood samples were collected by the time during the period of 60 to 120 minutes. Blood samples were analyzed and drug contents were determined. The plasma profiles of antiepileptic drugs were obtained and compared. The plasma profiles of antiepileptic drugs were found to be low when they were administered by IP route. It was concluded that the IP administration of antiepileptic drugs could not be an alternative route to IV administration.

Key Words: *Convulsion, anticonvulsant drugs, intraperitoneal route*

Antikonvülzan İlaçların İntraperitonal Yoldan Verilmeleri

Özet

Epilepsi veya epilepsi nöbeti ciddi beyin hasarlarına neden olabilir ve eğer fazla uzun sürerse geri dönüşsüz beyin harabiyetine neden olabilir, bu nedenle nöbetin süratle durdurulması oldukça önemlidir. Antiepileptik ilaçlar hastalara intravenöz (IV) yolla verilebilir ancak nöbetler esnasında hastaya IV ulaşım hemen hemen imkansızdır ancak intraperitonal (IP) yol ile ilaç verilmesi mümkündür, ancak şimdiye kadar antiepileptik ilaçların IP yoldan verilmesi denenmemiştir. Bu nedenle, çalışmada antiepileptik ilaçların IP yoldan verilmelerinin mümkün olup olmadığı araştırılmıştır. Antiepileptik ilaçlar (diazem, fenitoin ve fenobarbital) tavşanlara ve köpeklere IV ve IP yoldan verilmiş ve 60 ila 120 dakikalık süreler zarfında kan örnekleri toplanmış ve analiz edilerek kanlardaki etkin madde içerikleri belirlenmiş ve plazma profilleri elde edilerek karşılaştırılmıştır. Antiepileptik ilaçların IP yoldan verildiklerindeki plazma düzeyleri düşük bulunmuştur. Sonuç olarak IP yoldan antiepileptik ilaçların verilmelerinin IV yola bir alternatif olamayacağı sonucuna varılmıştır.

Anahtar Kelimeler: *Konvülziyon, antikonvülsif ilaçlar, intraperitoneal yol*

Status epilepticus refers to prolonged seizures more than 20 minutes in duration or serial seizures that occur without intervening return of consciousness. Termination of status epilepticus in time may prevent or mitigate permanent neurologic damage associated with the seizure itself. In addition, early control of status epilepticus may reduce the need for more aggressive interventions (e.g., multiple anticonvulsant administration, endotracheal intubation, ICU admission, prolonged hospital stay). This should result in lower morbidity and less use of medical resources (1,2). Clinical and electrical seizure must be terminated rapidly. Typical therapy includes IV diazepam or lorazepam followed by phenytoin and barbiturates. IV access, however, is frequently difficult to achieve. 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 IP route is an alternate way to administer fluids (3). There is no study available in the lit-

erature investigating the intraperitoneal administration of antiepileptic drugs. The purpose of this study was to determine the possibility of IP administration of diazepam, phenytoin and phenobarbital and to determine and compare their plasma levels.

Materials and Methods

Materials

Diazepam obtained from Deva Drug Company (Barbaros street, Ak İŞ Hanı, No: 64, Zincirlikuyu, İstanbul, Turkey), phenytoin obtained from EWL Eczacıbaşı-Warner Lambert Drug Company (Büyükdere street, 185 Levent, İstanbul, Turkey) and Phenobarbital was from Bayer Türk Chemical Industry (Davutpaşa street, No: 24, Topkapı, 34020, İstanbul, Turkey). Other chemicals and reagents were of analytical grade.

Analysis of diazepam in plasma

Diazepam was analyzed by High Pressure Liquid Chromatography (HPLC) (Hewlett Packard-model 1050). 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.

Analysis of Phenobarbital and Phenytoin 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 or Phenytoin were determined using fluorescence polarization immunoassay (FBIA; TDx, Abbott Diagnostics, North Chicago, IL, USA). Serum samples containing only unbound fractions of Phenobarbital or 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 Phenobarbital or Phenytoin were < 5.0 %.

IV Administration of Anticonvulsant Drugs

Anticonvulsant drugs were diluted with normal saline to a 1:1 ratio and infused over 10 seconds to the rabbits and dogs. Subsequent to the injection, the needles were flushed with 5 ml normal saline. The dose was 20 mg/kg for phenobarbital, 15 mg/kg for phenytoin and 0.2 mg/kg for diazepam. Plasma samples were collected by the time from the vein and analyzed.

Peritoneal Administration of Anticonvulsant Drugs

Anticonvulsant drugs were administered by IP route to the rabbits and dogs by injection with doubled dose of IV injection. Plasma samples were collected by the time from the vein and analyzed.

Results

Anticonvulsant drugs were administered to rabbits and dogs by IV and IP injection. Figure 1,2 and 3 show the blood diazepam, phenobarbital and phenytoin concentrations after IV and IP injections in rabbits. Three replicates were done for each drug.

Figure 4,5 and 6 show the blood diazepam, phenobarbital and phenytoin concentrations after IV and IP injections in dogs. Three replicates were done for each drug.

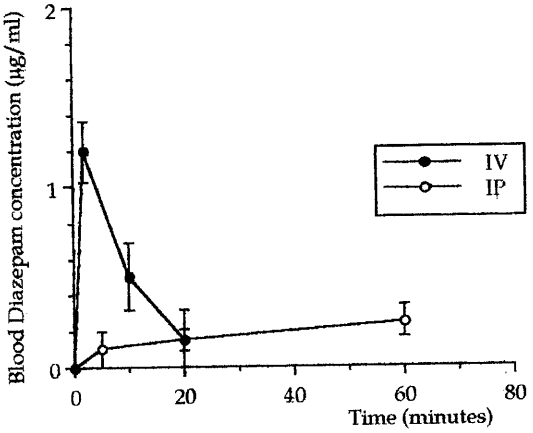

Figure 1. Blood Diazepam concentrations in rabbits after IV and IP administrations (n=3, error bars represents SEM).

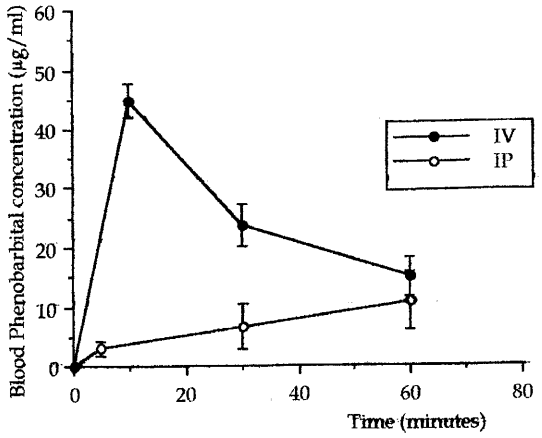

Figure 2. Blood Phenobarbital concentrations in rabbits after IV and IP administrations. (n=3, error bars represents SEM).

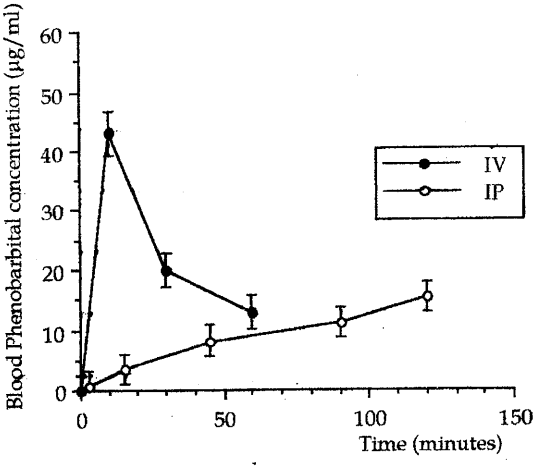

Figure 5. Blood Phenobarbital concentrations in dogs after IV and IP administrations (n=3, error bars represents SEM).

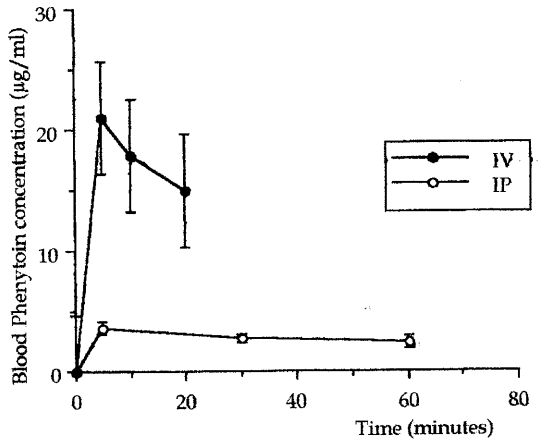

Figure 3: Blood Phenytoin concentrations in rabbits after IV and IP administrations. (n=3, error bars represents SEM).

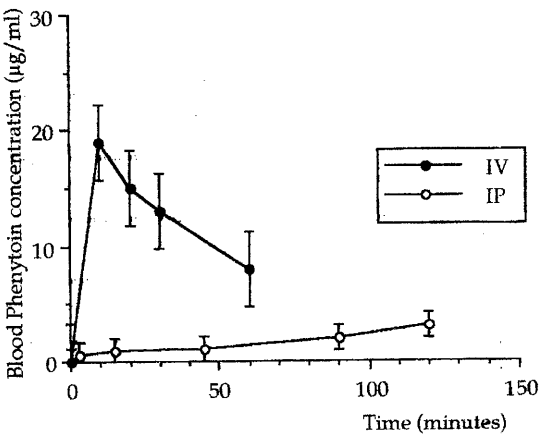

Figure 6. Blood Phenytoin concentrations in dogs after IV and IP administrations (n=3, error bars represents SEM).

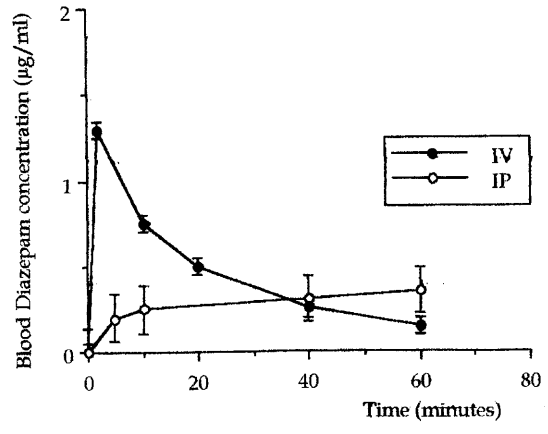

Figure 4. Blood Diazepam concentrations in dogs after IV and IP administrations (n=3, error bars represents SEM).

All the results indicated that peritoneal route provided insufficient amount of the anticonvulsant drugs to the circulation at the beginning but, later on it started to increase, but it was found to be ineffective comparing to IV injection results.

When anticonvulsant drugs were introduced rabbit or dog through the IP route, the plasma level of the drug increases much slowly comparing to IV results which indicates the partition characteristic of drug forces the drug to penetrate from the peritoneal membrane but it was not found as quick as needed. Their partition coefficients (Log-P) and molecular weights (MW) were calculated using ACD-Log P computer software[4] as follows:

Drug	MW	Log-P
Diazepam	284,74	2,96±0,46
Phenobarbital	232,24	1,71±0,28
Phenytoin	252,27	2,52±0,38

Discussion

When the patients present in status epilepticus or seizure, rapid antiepileptic therapy is required. If IV access is not readily available, other routes must be used. A variety of techniques have been investigated for the emergency administration of medications. These include intracardiac, intratracheal, sublingual, and even intradermal clysis. The utility of these techniques has been limited by technical difficulties, complications, or inadequate serum levels of medications. Unfortunately, drugs administered by the intramuscular and rectal routes are absorbed erratically. The IP route was found to be accessible and convenient during status epilepticus at the beginning but lower plasma profiles were obtained when anticonvulsant drug was administered by IP route comparing with the IV administration results. The molecular weights and octanol/water partition coefficients which indicates the affinity of the drugs to the lipoidal membranes were found to be similar for all anticonvulsant drugs tested. Their blood profiles for both administrations were found to be similar as well.

As a result IP route was not found to be useful and an alternative route to IV route especially in emergency case or when very rapid absorption is needed.

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