

INTRAVENOUS VALPROIC ACID FOR THE TREATMENT OF STATUS EPILEPTICUS AND SEIZURE CLUSTERS

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Abstract

Status epilepticus (SE) and seizure clusters (SCs) are emergency situations, which require immediate and effective treatment. This study aimed to investigate the efficacy and tolerability of intravenous (IV) administration of Valproic acid (IV VPA) in the treatment of SE and SCs. All patients treated in our department with IV VPA between January 2009 and February 2010, were retrospectively analyzed. Indications for IV VPA were SCs and SE refractory to first line therapy (benzodiazepines). Dose, responsiveness and adverse events were evaluated. 31 patients (19 males and 12 females, median age 54.2 years), were included in the study. Twenty one patients presented primary generalized SCs, 6 had focal motor *status epilepticus* and 4 had focal seizures with secondary generalization. All had previously been unsuccessfully treated with intravenous infusion of Diazepam. The treatment protocol implied a 25mg/kg b.w. of IV VPA loading dose over 30 minutes, followed by continuous infusion of 100 mg/h for at least 24h, continued by oral administration. In 80% of the cases (25 of 31), seizures stopped within 6 h, and general anesthesia was not required. Four patients (12%) required general anesthesia and 2 patients were resistant to all therapeutic attempts and died. SE was symptomatic in all cases, 16 with stroke, traumatic 6, toxic 4, infectious 3 and tumors 2. No serious side effects were reported considering that relevant medical history included cardiac arrhythmias, respiratory distress and hepatic disease. IV VPA proved to be a safe, effective treatment of *status epilepticus* and SCs, especially in patients with co-morbidities (cardiovascular diseases and respiratory insufficiency).

Rezumat

Statusul epileptic și crizele epileptice subintrante reprezintă situații de urgență neurologică majoră, care necesită tratament prompt și eficient. Studiul prezentat analizează eficiența și tolerabilitatea valproatului administrat intravenos în tratamentul statusului epileptic și al crizelor subintrante. Au fost analizați retrospectiv toți pacienții admiși în clinica noastră și tratați cu valproat intravenos în perioada ianuarie 2009 - februarie 2010. Indicațiile de tratament au fost crizele epileptice subintrante și statusul epileptic refractar la tratamentul intravenos cu benzodiazepine. Au fost evaluate dozele, răspunsul terapeutic și reacțiile adverse. Au fost incluși în studiu 31 de pacienți. Douăzeci și unu de pacienți au

prezentat convulsii tonico-clonice primar generalizate cu caracter subinrant, 6 cu status epileptic focal motor și 4 au prezentat convulsii focale cu generalizare secundară. Toți pacienții au fost anterior tratați fără succes cu diazepam intravenos. Protocolul de tratament a fost reprezentat de inițierea cu 25mg/kg corp a dozei de încărcare pentru valproat timp de 30 minute, urmată de perfuzie continuă de 100 mg / h pentru cel puțin 24 de ore, continuat apoi per os. În 80% din cazuri, convulsiile au fost oprite în decurs de 6 ore, iar anestezia generală nu a fost necesară. Patru pacienți (12%), au necesitat anestezie generală, iar 2 pacienți au fost refractari la toate încercările terapeutice și au decedat. Statusul epileptic a fost simptomatic în toate cazurile, 16 prin accident vascular cerebral, 6 posttraumatice, 4 toxice, 3 infecțioase, două tumorale. Nu au fost raportate reacții adverse serioase având în vedere istoricul medical relevant de aritmii cardiace, detresă respiratorie și insuficiență hepatică. Administrarea intravenoasă de valproat s-a demonstrat a fi un tratament sigur și eficient pentru cuparea statusului epileptic și al crizelor subintrante, mai ales la pacienții cu comorbidități (boli cardiovasculare și insuficiență respiratorie).

Keywords: *status epilepticus*, valproic acid

Introduction

Status epilepticus (SE) and serial attacks also known as seizure clusters (SCs) represent major neurological emergencies and the mortality rate for SE is high, ranging from 3 to 25 %, depending on the cause and comorbidity [1]. Most recent literature agrees that any convulsions lasting for more than 5 minutes, or two or more convulsions in a 5-minute interval without return to preconvulsive neurological baseline, are sufficient to qualify for the diagnosis of SE, (traditional requirement for seizures to last for a minimum of 30 minutes has been abandoned by most authors) [2]. SCs often end in SE, in which a series of grand mal seizures follow one another with no conscious interval. The etiology is considered the major prognostic factor in SE [3]. Anoxia, stroke, central nervous system infections and metabolic dysfunctions are associated with the worst prognosis, but low plasmatic levels of antiepileptic drugs (AEDs) in epileptic population, alcohol intoxication and traumatic brain injury predict a better outcome [1]. This study aimed to investigate the efficacy and tolerability of intravenous Valproic acid (IV VPA) in the treatment of SE and SCs which are considered emergency situations, requiring immediate and effective treatment in the neurological intensive care units.

Materials and Methods

We retrospectively analyzed all the patients treated with IV VPA in the Neurology Intensive Care Department of Academic Emergency Hospital Sibiu, Romania between January 2009 and February 2010. The study was

approved by the Ethics Committee of the Hospital. Indications for IV VPA were SCs and SE refractory to the first line of therapy (benzodiazepines were immediately administered in the emergency room with intravenous diazepam 5 mg at a dose rate of 2 mg/minute IV, repeated after 10 minutes). Electroencephalographic monitoring was set for all the patients included in this study. Dose responsiveness and adverse events were evaluated. The treatment protocol was with 25 mg/kg b.w. of IV VPA loading dose over 30 minutes, followed by continuous infusion of 100mg/h for at least 24 hours, then oral administration through nasogastric tube. If seizures were not stopped, general anesthesia was performed, the anesthetic drug used was thiopental (the loading dose was 20 mg/kg b.w. IV slow *bolus* followed by 3–5 mg/kg b.w./hour IV via continuous infusion).

Results and Discussions

During a period of 14 months, we have identified a total number of 31 patients with SE treated with IV VPA. The mean age of patients was 52.4 years old. All patients had been previously unsuccessfully treated with Diazepam IV during the transportation and admission in our department. The treatment protocol implied a 25 mg/kg b.w. of IV VPA loading dose over 30 minutes, followed by continuous infusion of 100mg/h for at least 24 hours, then oral administration. In 81% of the cases (25 of 31 patients) seizures were stopped within 6 hours and general anesthesia was not required. In 13 % (4 patients) the general anesthesia was needed. The anesthetic drug of choice was thiopental (the loading dose of thiopental was 20 mg/kg b.w. IV slow *bolus* followed by 3–5 mg/kg b.w./hour IV via continuous infusion) (table I). Two patients (6 %) were resistant to all therapeutic attempts and died. Deaths were attributed to the underlying diseases – one case of encephalitis and one with cerebral metastasis. No serious adverse effects were reported as relevant underlying medical conditions included cardiac arrhythmias, respiratory distress and hepatic failure (all patients were permanently monitored in the intensive care unit). There were few temporary side-effects (slight transient increase of the ALT and AST transaminases was reported in 4 patients – 13%) with restitution after the IV VPA was finished. Typical adverse effects of standard AEDs for SE, such as respiratory and circulatory insufficiency, drug interaction or encephalopathy were not observed.

Table I

Etiology, type of seizure and evolution under treatment in the studied group		
	Total (31)	Total (%)
Gender		
Male	19	61.3
Female	12	38.7
Mean age	52.4	
Etiology		
Stroke	16	52.0
Trauma	6	19.0
Toxic	4	13.0
Infectious	3	10.0
Tumor	2	6.0
Type of seizure		
Primary generalized serial attacks	21	67.7
Focal motor status epilepticus	6	19.4
Secondary generalized focal seizures	4	12.9
Evolution under treatment		
Seizures stopped within 6h	25	81.0
Required anesthesia	4	13.0
Death (1 tumor and 1 encephalitis)	2	6.0

Benzodiazepines are widely accepted as the drugs of choice for initial therapy in the early stage of *status epilepticus* [4]. The effectiveness of benzodiazepines and especially diazepam decreases very rapidly probably because of decrease of sensitivity of GABA receptors. A down-regulation mechanism is supposed due to neuronal membrane modifications during a seizure [4]. Cited disadvantages of diazepam are short redistribution half-time (less than 1 h) and large volume of distribution (1-2 L/kg) [5]. These pharmacologic properties of diazepam decrease the brain concentration rapidly after initial intravenous administration, leading to potentially high rates of seizures recurrence. Repeat boluses of diazepam, can lead to significant accumulation and progressively greater peak levels. This may result especially in respiratory depression, and cannot be recommended [4]. On the other hand, lorazepam has a lesser volume of distribution and a smaller lipid solubility. Because of these properties the peaks levels are reached within 30 minutes (with a therapeutic level reached as rapid as diazepam) and the half-life time is considerably longer (2-3 h) [5]. The

longer initial duration of action and a smaller risk of cardiorespiratory depression make lorazepam the drug of choice in SE. A restriction in the use of intravenous lorazepam is its absence in the Romanian pharmaceutical market. If the therapy with benzodiazepines failed (the seizures continue after 30 minutes after the first benzodiazepine was given), the patient is situated in the stage of established status epilepticus. According to the guidelines, it is recommended to administer phenytoin (or fosphenytoin). As an alternative it is recommended to administer valproate or levetiracetam. The disadvantages of phenytoin are that it crystallizes and precipitates in solutions and it may cause thrombophlebitis (with extravasation), it is a potent enzyme inducer and has variable biological effects related to genetic variations of CYP2C9 [6]. Its vehicle, propylene glycol, can cause hypotension. Cardiac monitoring is required for both phenytoin and fosphenytoin and the dosing units of the drug are confusing and have caused problems in practice [5]. Intravenous VPA administration in SE and SCs, given in bolus, was well tolerated locally (no irritation signs to injection site). VPA appears to be safe in patients with co-morbidities. No cardiovascular changes were noted in these patients, no hemodynamic changes also. Even to high doses of VPA with rapid infusion, no respiratory depression was noticed. Four patients (13 %) were non responders to any kind of AED's and they required pharmacological coma induction with thiopental. IV administration of VPA efficacy is dependent on time lapse between symptoms and VPA treatment and administration of a sufficiently high loading dose [1]. Other studies suggested that the efficacy of VPA is comparable to that of IV diazepam; seizure activity remitted in 80% of children to whom IV VPA was given and 85% on IV diazepam. The median time needed to control the refractory SE was significantly shorter with VPA (5 minutes) than diazepam (17 minutes) [7, 8]. In a randomised open study [7], non-responding SE to diazepam, was treated with IV VPA at doses of 20 mg/kg b.w. or phenytoin 20 mg/kg b.w. in 50 patients for each group. Treatment success was 88% for IV VPA and 84% for the patients treated with phenytoin. These results are concordant with our study. Some of the authors suggest higher doses (25 – 45 mg/kg b.w.) of IV VPA [9]. Limitation of this study are due to the small and heterogenous sample size, making possible just a descriptive statistic.

Conclusions

Intravenous VPA proved to be a safe, effective treatment of *status epilepticus* and SCs, especially in patients with co-morbidities

(cardiovascular disease and respiratory insufficiency) and side effects were lower in comparison with other AEDs used in SE or SCs as confirmed in other recent studies [10]. The percent of seizure free outcome within 6 hours was relatively high in our group, which suggests that IV VPA for SE and SCs can be an effective treatment, but this must be assessed in large group studies to obtain more relevant data.

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