Intravenous Valproate for Seizures in 137 Taiwanese Children – Valproate Naive and Non-naive

Yu-Ching Chang, Jainn-Jim Lin, Huei-Shyong Wang, Min-Liang Chou, Po-Cheng Hung, Meng-Ying Hsieh, Kuang-Lin Lin

Abstract-

Purpose: Valproate has been widely used in controlling various kinds of seizures. Intravenous forms of valproate control seizures in a more rapid and efficacious pattern than oral forms. We evaluated the effectiveness and adverse effects of intravenous valproate for controlling seizures in Taiwanese children under 18 years old.

Methods: Retrospective chart reviews were performed on 137 pediatric patients receiving valproate infusion from January 2003 to December 2006. Patients were divided into 4 groups as follows: (1) previous use of other antiepileptic drugs (AEDs) (n=59), (2) previous use of oral valproate (n=8), (3) previous use of other AEDs and valproate (n=32), (4) first time use of valproate (n=38). The indications for using intravenous valproate include status epilepticus, repetitive seizures, prophylactic use for brain operations or in cases where oral administration was not feasible due to medical problems.

Results: The mean age was 8±6.22 years old and the average dose was 31.2±26.45 mg/kg/day. The mean duration of usage was 7.8±6.99 days. Eight patients failed to respond to intravenous valproate and the AED was shifted to other drugs. Thirty-two patients achieved successful seizure control after adding other AEDs following intravenous valproate. The seizure control rate in our study was 71%, and six patients died of complications associated with an underlying disorder. An allergic reaction (skin rash) was found in 1 patient, while no serious adverse effects were noted in our patients.

Conclusion: Intravenous valproate is effective and safe in controlling seizures in children who are either valproate naive or not.

Key Words: valproate, intravenous, epilepsy, seizure

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INTRODUCTION

Early seizure control prevents neurological sequelae and improves outcomes. Intravenous antiepileptic drugs (AEDs) can achieve seizure control in a more rapid and efficacious way than oral AEDs. The availability of

From the Division of Pediatric Neurology, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan.
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Reprint requests and correspondence to: Kuang-Lin Lin, M.D. Division of Pediatric Neurology, Chang Gung Children's Hospital, No. 5, Fu-Shin Street, Kwei-Shan, Taoyuan, 333, Taiwan.
E-mail: lincgh@adm.cgmh.org.tw

intravenous valproate since the 1980s has provided an alternative to phenobarbital and phenytoin, since these AEDs cannot be used in all patients, including those with allergic reaction to phenobarbital and some forms of progressive myoclonus epilepsy[1]. Valproate injection was approved in the United States in 1996 for intravenous use in epileptic patients for whom oral administration of valproate was temporarily not feasible[2]. The bioavailability and tolerance of intravenous valproate, when infused for 60 minutes every 6 hours, are similar to those of oral valproate[3]. Valproate is a simple branched-chain carboxylic acid with a chemical structure very similar to that of short-chain fatty acids. Although its mechanism of action is not fully elucidated, valproate is thought to potentiate gamma-aminobutyric acid-ergic (GABA-ergic) functions by increasing both synthesis and release of GABA[4]. Both clinical experience and many studies have demonstrated that valproate is a broad spectrum AED, which is useful across multiple types of seizures and epileptic syndromes. Also, the lack of serious cardiovascular, neurological, or local adverse effects supports the use of intravenous valproate in emergent situations.

To evaluate the efficacy and safety of intravenous valproate used in children, we retrospectively reviewed the charts of children who had received intravenous valproate.

SUBJECTS AND METHODS

The charts of 186 pediatric patients treated between January 2003 to December 2006 with valproate infusion at Chang Gung Children's Hospital were retrospectively reviewed. Approval for this study was obtained from the institutional review board. Full explanation for the guardians had been provided before intravenous valproate was used. Forty-nine patients were excluded due to insufficient clinical data or if only a single intravenous bolus of valproate was administered. A total of 137 patients were enrolled in our study. We analyzed the patients' seizure types, current AEDs, indications, durations and dosages of valproate usage, methods of administration, results of seizure control, and side effects. We divided patients into 4 groups as follows: (1) previous use of other AEDs (n=59), (2) previous use of oral valproate only (n=8), (3) previous use of other AEDs and valproate (n=32), (4) first time use of valproate (n=38). "Seizure control" was defined as: (1) reduction of seizure frequency to less than 30% over a 3 day period in refractory repetitive seizures; or (2) interruption of clinical seizure activity within less than 15 minutes followed by a seizure free period during intravenous therapy for at least 12 hours in status epilepticus; or (3) no clinical seizure activity for 7 days in patients after brain surgery or in those who could not feasibly receive oral valproate.

We examined whether patients suffered from side effects of valproate treatment (gastrointestinal upset, dizziness, headache, increased appetite, hepatotoxicity, hyperammonemia, and thrombocytopenia), including their duration and severity. Indications for intravenous valproate usage in our patients included status epilepticus (continuous or repeated seizure activity for more than 20 minutes without recovery of consciousness), refractory repetitive seizures (more than 2 times per day), prophylactic use for brain operations (brain tumor, intracranial hemorrhage, arteriovenous malformation), or oral intake not feasible due to other medical problems.

RESULTS

Among the 137 children studied, there were 68 boys and 69 girls, ranging in age from 2 months to 18 years (average 8 ± 6.2 years). The seizure types, according to the patient's clinical manifestation and electroencephalogram (EEG) reports, included primary generalized tonic-clonic seizures (charts reported seizure patterns as generalized tonic-clonic and EEG also showed generalized epileptiform discharge; n=28), secondary generalized tonic-clonic seizures (charts reported seizure patterns as generalized tonic-clonic with initial focal onset and EEG revealed focal epileptiform discharge; n=51), simple partial seizures (n=22), complex partial seizures (n=15), myoclonic seizures (n=2), infantile spasms (n=6), and mixed types (more than one of the seizure types were reported; n=2). Indications for intravenous valproate

usage in our patients included status epilepticus (n=17), refractory repetitive seizures (n=101), prophylactic use for brain operations (n=11), or oral intake not feasible due to medical problems (n=8). The average dose was 31.2±26.45 mg/kg/day. Five patients received valproate higher than 60 mg/kg/day to achieve seizure control, and 2 of them used valproate as high as 100mg/kg/day. No severe side effects related to valproate treatment in these 5 patients were observed, although 1 of these patients subsequently died of sepsis. The mean duration of usage was 7.8±6.99 days. The mean therapeutic level (trough) was 67±26.67 ug/mL. Methods of administration included intermittent (n=103) or continuous intravenous infusion (n=34).

Eight patients failed to respond to valproate and were administered other AEDs. Thirty-two patients achieved a satisfactory level of seizure control after adding other AEDs (lamotrigine, topiramate, gabapentin, vigabatrin, carbamazepine, pyridoxal phosphate, phenobarbital, and phenytoin). A total of ninety-seven patients (71%) in our study achieved successful seizure control. There was no significant difference between intermittent or continuous intravenous infusion in regard to seizure control (77% vs 50%, respectively). Six patients died of complications from underlying disorders. An allergic reaction (skin rash) was found in 1 patient. The common side effects of valproate (nausea, stomach irritation, increased appetite, and dizziness) were seen in 30 patients but were mild and transient. However, there were no patients who exhibited severe side effects such

Table 1. *Comparison of four groups of patients using intravenous valproate*

	previous use of other AEDs (n = 59)	previous use of oral valproate (n = 8)	previous use of other AEDs+valproate (n = 32)	first time use of valproate (n = 38)
Age (y/o)	6.27	6.25	9.34	10.47
Indications (n)				
Repetitive seizures	43 (74%)	5 (62%)	26 (81%)	27 (71%)
Status epilepticus	15 (24%)	0	2 (6%)	0
NPO	1 (2%)	3 (38%)	4 (13%)	0
Prophylactic	0	0	0	11 (29%)
Dosage (mg/kg/d)				
Mean	35.4	34.4	31.9	23.1
Range	17~100	20~70	12~64	11~40
Blood level (ug/mL)	$^{+}$N=37	N=5	N=25	N=8
Mean	65.5	65.6	65.1	72.9
Range	20~150	38~61	30~122	24~98
Duration (days)				
Mean	10.8	5.6	7.8	7
Duration	2~48	3~11	3~43	1~30
Administration (n)				
Continuous	25 (42%)	1 (13%)	6 (19%)	2 (5%)
Intermittent	34 (58%)	7 (87%)	26 (81%)	36 (95%)
Seizure control rate (n)				
Total	36 (61%)	6 (75%)	28 (88%)	27 (71%)
Exclude NPO & prophylactic	35 (60%)	3 (60%)	24 (86%)	16 (59%)
Continuous administration	11 (44%)	0 (0%)	6 (100%)	0 (0%)
Intermittent administration	24 (71%)	6 (86%)	22 (85%)	27 (75%)

AED: antiepileptic drugs;

+: numbers of patients for whom blood drug level was checked

as extreme hepatotoxicity, thrombocytopenia with abnormal bleeding, or hyperammonemia (ammonia > 150 mmole/dL).

Among the 4 groups of patients (Table 1) studied, the seizure control rate was the lowest (61%) in group 1 which included patients who had previously used other AEDs. The seizure control rates in group 2 and group 3 were 75% and 88%, respectively, which were higher than group 1. This finding was understandable because patients in these 2 groups were responsive to oral valproate. In group 4, the seizure control rate was 71%, which was also higher than group 1. These findings indicate that intravenous valproate was effective as a first line treatment of seizures. There was no significant difference in seizure control rates among the 4 groups after we excluded patients whose indications for intravenous valproate were either because oral intake was unfeasible or for prophylactic use before brain surgery ($p < 0.05$, table 1). Also, in the 11 patients with brain surgery, no one experienced a seizure with intravenous valproate prophylaxis.

Eight patients failed to respond to intravenous valproate and were shifted to other AEDs (Table 2), and all except one of these patients were younger than 3 years of age. Days of admission all exceeded 2 weeks except for one patient who died on the fifth day of admission (patient 5), and all patients were admitted to the intensive care unit. Seizure types included four primary generalized-tonic-clonic seizures, three secondary generalized tonic-clonic seizures, and one patient presenting with infantile spasms. Indications for intravenous valproate were all repetitive seizures except in one patient (patient 5, who presented with status epilepticus). The dosage ranged from 30 to 60 mg/kg/day. Three of 8 patients received continuous intravenous infusion.

Seventeen patients in our study received intravenous valproate due to status epilepticus (Table 3). The seizure control rate was 59%, which was slightly lower than the group of patients whose indication for intravenous valproate was repetitive seizures (65%). The age ranged from 15 months to 16.75 years old. Encephalitis was diagnosed in 7 patients. Patient 1 was a case of Leigh disease, and her seizures were intractable even after a

Table 2. *Characteristics of eight patients who failed to respond to intravenous valprote*

	Gender	Age	BW (kg)	Diagnosis	Seizure type	Indication	Duration of admission (days)	Dosage (mg/kg/d)	Level (ug/mL)	Previous drug used	Duration of drug use (days)	Methods of administration
1	F	1y6m/o	9.8	EDH,meningitis	Primary GTC	repetitive	29	30	95.6	TPM,PHT	8	Every 6 hrs
2	M	4m/o	5	infantile spasm	infantile spasms	repetitive	15	48	NA	TPM, PB	8	Continuous
3	F	1y6m/o	10	meningoencephalitis	Secondary GTC	repetitive	17	25	NA	PB, PHT	2	Continuous
4	M	2y/o	10.5	oligodendroglioma	Secondary GTC	repetitive	24	48	71	PB	17	Every 6 hrs
5	M	2y5m/o	13	encephalitis	Primary GTC	status	5	45	NA	PB,PHT	2	Continuous
6	F	11y/o	22	Cerebral palsy	Secondary GTC	repetitive	58	60	44	VGB, La tab	22	Every 6 hrs
7	M	1y2m/o	12	SDH	Primary GTC	repetitive	17	30	41	Nil	7	Every 6 hrs
8	F	10m/o	8	SDH,EDH	Primary GTC	repetitive	32	37	NA	Nil	1	Every 6 hrs

Table 3. *Characteristics of 17 patients with status epilepticus*

Patient No.	Gender	Age	Diagnosis	Seizure type	BW (kg)	Dosage (mg/kg/day)	Drug level (ug/dl)	Previously used AEDs	Duration (days)
1	F	2 m/o	Leigh disease	CPS	3.7	100	72	PB,PHT	4
2	F	1y3m/o	Epilepsy	GTC (s)	9.5	30	84	PB,PHT	13
3	M	2y5m/o	Encephalitis	GTC (p)	13	45	NA	PB,PHT	2
4	F	2y2m/o	Encephalitis	GTC (s)	11	20	NA	PB,PHT	9
5	M	1y9m/o	Gaucher disease	GTC (s)	9	100	29	PB,LMT,CNZ	29
6	M	3 y/o	Encephalitis	GTC (p)	20	40	77	PB,PHT,CMZ	33
7	F	3y2m/o	Encephalitis	GTC (p)	14	30	77	PB,PHT	9
8	F	4 y/o	Cerebral palsy	SPS	9.7	24	NA	TPM	2
9	F	4y6m/o	Epilepsy	GTC (s)	22	12	48	PHT	4
10	F	5y2m/o	Encephalitis	GTC (s)	17.6	56	80	PHT	22
11	F	5y3m/o	Epilepsy	GTC (s)	20	24	44	CMZ,PB,TPM,LA	11
12	M	6y8m/o	Medulloblastoma	GTC (p)	17	25	64	PB,PHT	19
13	M	6y7m/o	Encephalitis	GTC (p)	18	25	54	PB,PHT,pyridoxal,	10
14	F	7y4m/o	Cerebral palsy	GTC (s)	20	30	89	PB,PHT	2
15	F	16y8m/o	Encephalitis	GTC (p)	47	48	62	PB,PHT	7
16	M	9 m/o	Infantile spasm	infantile spasm	8	50	50	valproate,PB	3
17	F	8 m/o	Lissencephaly	GTC (s)	9	27	NA	valproate,PB,PHT	4

GTC: generalized tonic-clonic; SPS: simple partial seizure; CPS: complex partial seizure; P: primary; S: secondary; NA: not available; AEDs: anticonvulsants; TPM: topiramate; PHT: phenytoin; PB: Phenobarbital; CMZ: carbamazepine; LMT: lamotrigine; CNZ: clonazepam; LA: la tab

valproate dose as high as 100 mg/kg/day. She eventually died of sepsis. For the others, the intravenous valproate dosage ranged from 12-56 mg/kg/day. Thirteen patients received intravenous valproate by continuous infusion, and the drug levels were all within the therapeutic range (50-100 ug/dL)

DISCUSSION

Although the clinical efficacy of valproate in children has been well established, little data exists regarding the use of intravenous valproate in children with epilepsy[5]. In our study, we examined a series of children with epilepsy who were valproate-naive or valproate non-naive. Among the different situations involving previous valproate usage, we found that intravenous valproate was consistently efficacious for seizure control.

In our study, seizure control rates among patients using intravenous valproate in the group presenting with repetitive seizures and status epilepticus were 65% and 59%, respectively, which was similar to previous studies. In the four studies examining intravenous valproate use in children reviewed by Aldenkamp et al, which included a total of 93 patients with status epilepticus, efficacy rates ranged from 58% to 100%[6]. Czapinski and Terezynski1 reported an 80% success rate in interrupting status epilepticus in a series of 20 adult patients using intravenous valproate[7]. In addition, Peters and Pohlmann-Eden reported a 85.6% success rate in controlling status epilepticus in a series of 102 adult patients using intravenous valproate[8], and Limdi et al stated the overall efficacy of valproate for controlling status epilep-

Table 3. *(continuous)*

Patient No.	Methods of administration	Add other AEDs	Result
1	Every 8 hrs	LMT	Expire
2	continuous	LMT	Seizure control
3	continuous	None	Expire
4	continuous	None	DC valproate (allergy)
5	continuous	None	Seizure control
6	Every 8 hrs	Pyridoxal	Seizure control
7	continuous	Pyridoxal	Seizure control
8	continuous	None	DC valproate (no attack)
9	Every 8 hrs	None	Seizure control
10	continuous	PBT	Seizure control
11	Every 6 hrs	None	Seizure control
12	continuous	None	Expire
13	continuous	None	Seizure control
14	continuous	None	Seizure control
15	continuous	None	DC valproate (cortical silence)
16	continuous	None	Seizure control
17	Every 8 hrs	None	Seizure control

ticus was 63.3%[9]. Notably, most of these previous studies examined the efficacy of intravenous valproate for status epilepticus. However, our study also showed the efficacy of this AED on patients undergoing brain surgery or those in a condition where oral intake was not feasible.

Valproate-induced hepatotoxicity has been described as four distinct subtypes, including a transient elevation of liver enzymes, hyperammonemia, toxic hepatitis, and a Reye-like syndrome[4]. Many reports had indicated that the risk of hepatotoxicity is greatest for patients younger than 2 years, whereby valproate is associated with hepatotoxicity at rates of up to 1/800 in children less than 2 years of age[4]. In our study, all but one patient who failed to respond to intravenous valproate were younger than 3 years old. Since the safety and effectiveness in pediatric patients under age 3 have not been well established, the use of valproate in this age group should be more cautious. The most common side effects of valproate (nausea, stomach irritation, increased appetite, and dizziness) were seen in 30 patients but were mild and transient. There were no patients, including those receiving higher doses of valproate, who exhibited severe side effects such as hepatotoxicity, thrombocytopenia with abnormal bleeding, severe hyperammonemia (ammonia > 150 mmole/dL) in our study. These results indicate that intravenous valproate could be considered as a first line AED in emergent conditions such as status epilepticus or in conditions where oral intake was not feasible.

In addition, there was no difference of efficacy between methods of administration (continuous or intermittent intravenous infusion). Most patient achieved seizure control in a dosage range of 30-60 mg /kg/day with blood trough levels ranging between 60-100 ug/mL. However, 5 patients required higher dosages (60-100 mg/kg/day) in order to achieve a seizure free state. Though high dose valproate (100-300 mg/kg/day) had been reported effective and safe in the treatment of infantile spasms in children[10], physicians should pay more attention to the side effects of valproate in such situations. Studies examining intravenous valproate administration in children have been few. Specifically, Morton et al investigated the safety of rapidly infused intravenous valproate in 18 children with seizures, and no obvious side effects were observed 5. Campistol et al stated that when valproate was given at 20 mg/kg as a single dose and with a maintenance dosing rate of 1 mg/kg/hour by intravenous infusion in 19 pediatric patients (1 day-7 years), status epilepticus was controlled in 58% of patients and reduced in 26%[11]. Yu et al retrospectively reviewed 40 pediatric patients with intravenous valproate loading for status epilepticus or acute repetitive seizures and showed a high success rate (100% for status epilepticus; 95% for acute repetitive seizures) without evidence of valproate-related systemic or local side effects[12]. Uberall et al reviewed 41 cases of children who had been refractory to treatment with intravenous diazepam followed by intravenous phenobarbital and phenytoin, but who then received intravenous valproate at loading doses of 20-40 mg/kg administered

over 1 to 5 min (and repeated if necessary) followed by infusions of valproate 5 mg/kg/hr, thereby stopping the clinical and bioelectric status epilepticus in 32 (78%) of 41 children[13]. Importantly, our study also revealed that intravenous valproate was effective and safe in children.

In conclusion, we presented one of the largest pediatric series demonstrating the safety and efficacy of intravenous valproate infusion in children with seizure disorders, including status epilepticus. In valproate-naive children with uncontrolled seizures, intravenous valproate may be considered as the first choice AED for emergent situations. For valproate non-naive children, intravenous valproate can serve as an acute rescue regimen when seizures become unresponsive to oral valproate. Furthermore, intravenous valproate for seizure prophylaxis in cases requiring brain surgery is also a good choice.

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