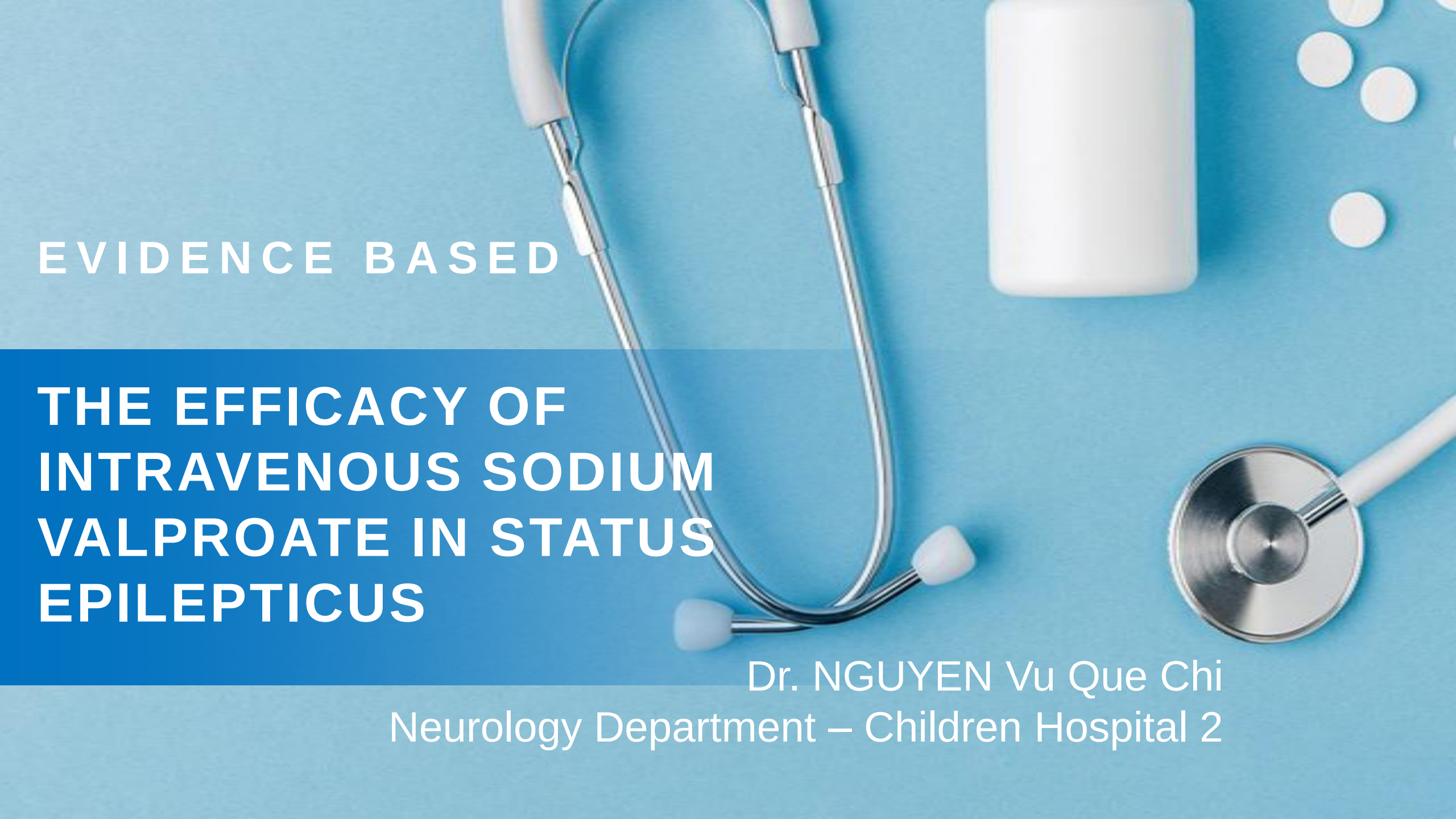

EVIDENCE BASED

THE EFFICACY OF INTRAVENOUS SODIUM VALPROATE IN STATUS EPILEPTICUS

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OVERVIEW

STATUS EPILEPTICUS

- Status epilepticus (SE) can be defined as “a condition characterized by an epileptic seizure that is so frequent or so prolonged as to create a fixed and lasting condition”.
- Tonic – clonic epileptic status is neurological emergency.

AMERICAN EPILEPSY SOCIETY
EPILEPSY CURRENTS
Reviews and Critical Analysis

Time Line	Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics
0-5 min Stabilization phase	1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam) 2. Time seizure from its onset, monitor vital signs 3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed 4. Initiate ECG monitoring 5. Collect finger stick blood glucose. If glucose < 60 mg/dl then Adults: 100 mg thiamine IV then 50 ml D50W IV Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W 6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels
	Yes — Does Seizure continue? — No
5-20 min Initial therapy phase	**A benzodiazepine is the initial therapy of choice (Level A)**: Choose one of the following 3 equivalent first line options with dosing and frequency: Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A) If none of the 3 options above are available, choose one of the following: Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR Intranasal midazolam (Level B), buccal midazolam (Level B)
	If patient at baseline, then symptomatic medical care
	Yes — Does seizure continue? — No
20-40 min Second therapy phase	**There is no evidence based preferred second therapy of choice (Level U)**: Choose one of the following second line options and give as a single dose Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose , Level U) OR Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose , Level U) If none of the options above are available, choose one of the following (if not given already) Intravenous phenobarbital (15 mg/kg, max dose, Level B)
	If patient at baseline, then symptomatic medical care
	Yes — Does seizure continue? — No
40-60 min Third therapy phase	**There is no clear evidence to guide therapy in this phase (Level U)**: Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).
	If patient at baseline, then symptomatic medical care

STATUS EPILEPTICUS

TREATMENT

Table 1. Medications for Status Epilepticus

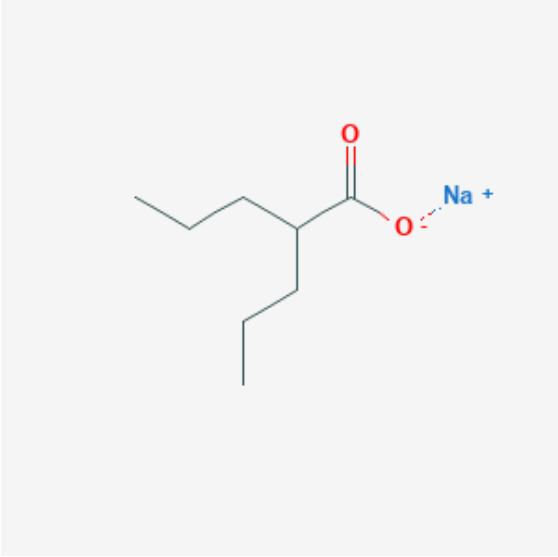
AED	IV Dosing	Alternative Dosing	Maximum Dosage
First-Line			
Diazepam	0.1-0.3 mg/kg IV q2 min	2-5 y: 0.5 mg/kg pr; 6-11 y: 0.3 mg/kg pr; ≥12 y: 0.2 mg/kg pr	30 days-5 y: 5 mg; >5 y: 10 mg
Lorazepam	0.1 mg/kg; may repeat in 5-10 min prn	NA	4 mg
Midazolam	0.2 mg/kg	13-40 kg: 5 mg IM; >40 kg: 10 mg IM; 0.2 mg/kg IN; 0.5 mg/kg buccal	10 mg
Second-Line			
Fosphenytoin	15-20 mg PE/kg IV; may give additional 5 mg/kg	NA	1,000 mg PE
Levetiracetam	20-60 mg/kg IV	NA	NA
Phenobarbital	15-20 mg/kg IV; may give additional 5-10 mg/kg	NA	40 mg/kg
Phenytoin	15-20 mg/kg IV; may give additional 5-10 mg/kg	NA	1,000 mg
Valproate	20-40 mg/kg IV; may give additional 20 mg/kg	1.5-3 mg/kg/min	40 mg/kg
Refractory			
Midazolam	0.2 mg/kg bolus followed by 2 mcg/kg/min	NA	10 mcg/kg/min
Pentobarbital	5-15 mg/kg; may give additional 5-10 mg/kg	50 mg IV initial dose	100 mg/dose
Propofol	1-2 mg/kg loading dose, then 20 mcg/kg/min	1 mg/kg IV followed by 0.5 mg/kg q3-5 min prn for sedation	NA

AED: antiepileptic drug; min: minute; NA: not applicable; PE: phenytoin equivalents; pr: per rectum.
Source: References 2, 8, 9, 12, 19, 22, 24.

VALPROATE

Click here to add text.

- Valproate was first made in 1881 and came into medical use in 1962.
- Increase levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in brain; may enhance or mimic action of GABA at postsynaptic receptor sites; may also inhibit sodium and calcium channels
- Metabolized by liver
- Half-life: 9-16 hrs
- Excretion: Urine (30–50%)



VALPROATE

CONTRAINDICATIONS

- Pregnancy
- Pre-existing acute or chronic hepatic dysfunction or family history of severe hepatitis,particularly medicine related
- Known hypersensitivity to valproate or any of the excipients used in the preparation
- Urea cycle disorders
- Hepatic porphyria
- Mitochondrial disease
- Pancreatitis

VALPROATE

DOSE

- Loading dose: 20 - 40mg/kg IV 3 - 5mg/kg/m, max 3000mg
- Maintenance dose: 30 – 60mg/kg/d (orally/ IV)

VALPROATE

ENVIDENCE OF EFICACY

- A systematic review of data from randomized and non-randomized controlled trials to evaluate the efficacy and safety of intravenous valproate for the treatment of status epilepticus. The pooled evidence included a total of 860 patients with various forms of status epilepticus treated with intravenous valproate. The overall response rate (control of status epilepticus) was 70.9 % (601/848; 95 % confidence interval [CI] 67.8–73.9)

- *Trinka E, Höfler J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. CNS Drugs. 2014 Jul;28(7):623-39.22*

VALPROATE

ENVIDENCE OF EFICACY

- A systematic evaluation of the published evidence-base for the efficacy of five antiepileptic drugs (lacosamide, levetiracetam, sodium valproate, phenytoin and phenobarbital) in benzodiazepine resistant convulsive status epilepticus. Eight studies describing treatment with intravenous sodium valproate in 250 benzodiazepine-resistant episodes were included in the meta-analysis. The meta-analysis was performed on a combination of different study designs, randomized with different comparators (phenytoin in Agarwal 200717, phenobarbital in Malamiri 201218), as well as observational studies. Three of the eight studies were in adults and Chen 2009 was in children and adults with status epilepticus resistant to IV Diazepam and intramuscular phenobarbital. The meta-analysis yielded a mean effect size for the efficacy of sodium valproate of 75.7% (95% CI: 63.7–84.8%). In this review, the efficacy of phenytoin was 50.2% (95% CI: 34.266.1%) and that of phenobarbital was 73.6% (95%CI: 58.3–84.8%).

Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure. 2014 Mar;23(3):167-74.1

VALPROATE

VS PHENYTOIN

- A randomized open-label trial of sodium valproate versus phenytoin in patients (adults and children) with status epilepticus which did not respond to first-line intravenous diazepam. Outcomes included seizure cessation, death, adverse effects and seizure recurrence within 24 hours. There was no difference in efficacy in terms of seizure cessation (44/50 in the sodium valproate group versus 42/50 in the phenytoin group) or seizure recurrence within 24 hours in both the groups (no patient in either group).

Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure 2007; 16: 527–532

VALPROATE

VS PHENYTOIN

AMERICAN EPILEPSY SOCIETY

- Sixty-eight patients with convulsive status epilepticus (SE) were randomly assigned to two groups to study the efficacy of sodium valproate (VPA) and phenytoin (PHT). Seizures were aborted in 66% in the VPA group and 42% in the PHT group. As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%. The side effects in the two groups did not differ. Sodium valproate may be preferred in convulsive SE because of its higher efficacy.

Sodium Valproate vs Phenytoin in Status Epilepticus: A Pilot Study, Misra UK, Kalita J, Patel R. 2007 Jul

VALPROATE

VS PHENYTOIN

The administration of sodium valproate and phenytoin respectively resulted in seizure control in 43 (78.18%) and 39 (70.90%) of the patients within 7 days of drug administration (p = .428). Seven-day mortality rate was similar in both groups (12.73% vs. 12.73%; p = .612). There was no significant difference in adverse effects between two groups.

Sodium valproate is preferred to IV PHT for treatment and control of SE due to its higher tolerability and lower hemodynamic instability.

Brain Behav. 2018 Mar 23;Sodium valproate compared to phenytoin in treatment of status epilepticus.

Amiri-Nikpour MR1, Nazarbaghi S1, Eftekhari P1, Mohammadi S2, Dindarian S2, Bagheri M2, Mohammadi H3.

VALPROATE

VS PHENOBARBITAL

- This was a randomized double blind study comparing the efficacy and safety of intravenous sodium valproate versus intravenous phenobarbital in children with status epilepticus not responding to intravenous diazepam.
- There was no difference in efficacy in terms of seizure cessation efficacy in terms of seizure cessation (27/30 in the sodium valproate group versus 23/30 in the phenobarbital group).
- Seizure recurrence within 24 hours was more in the phenobarbital (12/23) group as compared to the sodium valproate group (4/27).
- Clinically significant adverse effects occurred in 74% patients of the phenobarbital group and 24% patients of the valproate group ($p < 0.001$).

Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: a randomised trial. Eur J Paediatr Neurol 2012

VALPROATE

VS PHENYTOIN & PHENOBARBITAL

- Both phenobarbital and phenytoin are associated with a range of side-effects such as cardiac arrhythmias,hypotension, and respiratory depression (although the latter may be exacerbated due to the prior administration of benzodiazepines).
- Phenytoin in addition can cause serious skin reactions at the injection site. It should be administered slowly through a large vein, and cardiac monitoring is required (which is frequently not available in resource-poor countries).

VALPROATE

VS DIAZEPAM

- An open-label, randomized controlled study was conducted at a tertiary care teaching hospital to compare efficacy and safety of intravenous sodium valproate versus diazepam infusion for control of refractory status epilepticus.Refractory status epilepticus was controlled in 80% of the valproate and 85% of the diazepam patients. The median time to control refractory status epilepticus was less in the valproate group (5 minutes) than the diazepam group (17 minutes; P < .001). None of the patients in the valproate group required ventilation or developed hypotension, whereas in the diazepam group 60% required ventilation and 50% developed hypotension after starting diazepam infusion. No adverse effects on liver functions were seen with valproate.

Journal of Child Neurology October 1, 2007: Intravenous Sodium Valproate Versus Diazepam Infusion for the Control of Refractory Status Epilepticus in Children: A Randomized Controlled Trial

Vishal Mehta, MD, Pratibha Singhi, MD, FIAP, Sunit Singhi, MD, FIAP, FAMS

VALPROATE

VS DEAZEPAM

- It is concluded that intravenous sodium valproate is an effective alternative to diazepam infusion in controlling refractory status epilepticus in children and is free of respiratory depression and hypotension.

Journal of Child Neurology October 1, 2007: Intravenous Sodium Valproate Versus Diazepam Infusion for the Control of Refractory Status Epilepticus in Children: A Randomized Controlled Trial

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VALPROATE

ENVIDENCE OF SAFETY

As on 31st January 2006, a total of 517 medically confirmed adverse drug reactions in 224 patients receiving intravenous sodium valproate had been reported in the worldwide SanofiAventis post-marketing pharmacovigilance database since 1994.24 Given the estimated exposure to intravenous sodium valproate over the period (1 million units prescribed per year worldwide), the reporting rate for adverse events was less than one case per 100,000 administrations.

VALPROATE

ENVIDENCE OF SAFETY

The systematic review by Trinka et al 22 provides key evidence as to the safety of sodium valproate. In this study, evidence for the safety of intravenous sodium valproate was obtained from dedicated safety studies, adverse event reporting in the efficacy studies, individual case reports, and pharmacovigilance reporting. The incidence of adverse events was low overall (<10 %), mainly dizziness, thrombocytopenia, and mild hypotension, which was independent of infusion rates, and a good cardiovascular and respiratory tolerability even in high doses and fast infusion rates up to 30 mg/kg at 10 mg/kg/min. The most frequent reported side effects in uncontrolled studies and case series include nausea/vomiting, dizziness and sedation. No effect on respiratory function was noted. Mild hyperammonemia and mild thrombocytopenia have been reported in few patients.

IN SUMMARY

- Sodium valproate IV is an option in the treatment of status epilepticus resistant to initial treatment with benzodiazepines in children and adults as a second-line agent. The overall response rate (control of status epilepticus) was 75.7 %.
- Effective for all types of status epilepticus **(Level B)**
- DOSE: Loading dose: 20 - 40 mg/kg IV 3 - 5 mg/kg/m, max 3000mg

  Maintenance dose: 30 – 60mg/kg/d (orally/ IV)
- Well tolerated as a rapid IV infusion
- Free of respiratory depression and hypotension.

THANK YOU

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