The Role of Intravenous Valproate in Convulsive Status Epilepticus in the Future

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Valproate is a broad spectrum antiepileptic drug (AED), which is useful in all types of seizures either generalized or partial seizures. However, intravenous (i.v.) valproate is seldom considered as first line in treatment of convulsive status epilepticus (CSE) for the side effects of hepatitis and pancreatitis, although rare but occasionally fatal, especially in young children and elderly. Can i.v. valproate be the first choice AED for emergent situations?

INCIDENCE OF FATAL HEPATOTOXICY AND PANCREATITIS WITH VALPROATE IN DIFFERENT AGES

Hepatic failure resulting in fatalities has occurred in patients receiving valproate. Caution should be taken when administering valproate to children with a history of hepatic disease, receiving AED polytherapy, or with severe seizure disorders accompanied by mental retardation. Children under the age of three years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the conditions described above. In early report, fatal hepatotoxicity in patients receiving polytherapy is approximately 1:600 in age below 3 years, 1:8,000 from 3 to 10 years, 1:10,000 from 11 to 20 years, 1:31,000 between 20 and 40 years, and 1:107,000 above the age of 41 years. The risk is lower in patients with monotherapy: it varies between 1: 16,000 from 3 to 10 years and 1:230,000 from 21 to 40 years. Cases of acute, life-threatening hemorrhagic pancreatitis have been reported in both children and adults receiving valproate. Some cases have occurred shortly after initial use as well as after several years of use.[1]

CURRENT GUIDELINE FOR TREATMENT OF CONVULSIVE STATUS EPILEPTICUS IN DIFFERENT COUNTRIES

In Japan, the Research Committee on Clinical Evidence of Medical Treatment for Status Epilepticus in Childhood has a proposed guideline for the treatment of CSE in childhood. Initial management of seizures should be attempted mainly with i.v. diazepam, the second-line treatment involves i.v. midazolam followed by i.v. phenytoin if seizures persist, and the third-line treatment requires barbiturate coma.[2]

In France, as intravenous lorazepam not available, clonazepam, rectal diazepam or buccal midazolam as the best choice for initial therapy of CSE in infants and young children. Intravenous phenytoin / fosphenytoin and phenobarbital are the second-line drugs. Of the third line AEDs, high-dose midazolam infusion rather than thiopental to minimize serious side effects from barbitu-

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rate anesthesia.[3]

In London, Neville et al. had proposed an amended algorithm for the management of childhood CSE which includes prehospital treatment and simplified hospital treatment in the light of current information. Prehospital treatment includes rectal diazepam or buccal midazolam or i.v. lorazepam. Managements in emergent department includes i.v. lorazepam (if not given before) followed by i.v. phenytoin (ideally phosphenytoin) or i.v. phenobarbitone. If CSE still persists, intensive care with i.v. propofol or i.v. thiopentole should be applied.[4]

In 2009, a systematic review of management of prolonged seizures and CSE in childhood by Sofou et al. has found that buccal midazolam is efficacious and safe thanks to its convenient route of administration, which may serve as first-line in the treatment of prolonged seizures. Intranasal lorazepam is an effective, easy-to-use, and safe drug for prolonged seizures. Intravenous valproate exhibits favorable efficacy and safety profile as third-line in SE refractory to diazepam and phenytoin.[5]

For CSE in adults, Arif and Hirsch had suggested the following treatment algorithm: In the first 6-10 minutes, thiamine 100 mg i.v. followed by 50 ml of D50 i.v. unless adequate glucose known and lorazepam 4 mg i.v. over 2 minutes; if still seizing, repeat lorazepam i.v.; if no rapid i.v. access give diazepam 20 mg per rectal or midazolam 10 mg intranasally, buccally or intramuscular. If seizures persist in 10-20 minutes, begin fosphenytoin 20 mg/kg i.v. at 150 mg/min. If seizures persist in 10-60 minutes, one (or more) of the following 4 options: continuous i.v. midazolam, continuous i.v. propofol, i.v. valproate (40 mg/kg over ~10 minutes, if still seizing, additional 20 mg/kg over ~5 minutes), or i.v. phenobarbital.[6]

SAFETY AND EFFICACY IN I.V. VALPROATE IN CHILDREN

In general, i.v. valproate is still not accepted as a first line treatment for CSE, even in adults. Several studies in pediatric patients showed a high success rate of intravenous valproate in status epilepticus (SE)and acute repetitive seizures (ARS) without severe side effects.[7,8,9] However, most of the available data on the efficacy of i.v. valproate in treating SE come from non-comparative case series.

In a review by Trinka, he found that studies on i.v. valproate for SE including children and elderly patients with cardiovascular instability (who may be at increased risk for adverse reactions due to phenytoin/fosphenytoin), showed a low incidence of adverse events especially no hemodynamic adverse effects, even when valproate was administered at higher than recommended infusion rates. The incidence of adverse events in patients receiving i.v. valproate (mainly hypotension, dizziness, and thrombocytopenia) was low (less than 10%) and independent of infusion rate. Only few cases of acute valproate encephalopathy were reported and the pharmacovigilance data reveal no increased incidence of encephalopathy with the i.v. use.[10]

In Taiwan, Chang et al. had reported their experience of i.v. valproate for seizures in 137 local children (in this volume of Acta Neurologica Taiwanica). They concluded that i.v. valproate is effective and safe in controlling seizures in children, which can be used as the first choice in SE and ARS. In their study, the mean age of patients was 8 ± 6.22 years 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 i.v. valproate, probably related to the progressive underlying cerebral lesion, e.g. meningoencephalitis, brain tumor or subdural hematoma. Thirty-two patients achieved successful seizure control after adding other AEDs following intravenous valproate. The seizure control rate was 71%, and six patients died of complications associated with an underlying disorder. There was no serious adverse effect, except one case had skin rash.

FUTURE PROSPECTS OF I.V. VALPROATE IN CSE?

Can i.v. valproate take the place of phenytoin and benzodiazepam over and becomes the first choice AED in emergent conditions as suggested by Chang et al.? It depends on the effectiveness and side effects of these

AEDs.

It is well known that phenytoin is effective in the abortive treatment of ARS and SE. In 60-80% of patients, a response was noted within 20 minutes after the initiation of an infusion of phenytoin.[11] A double-blind, randomized trial in 384 patients with CSE, i.v. lorazepam (64.9%) was the most successful treatment to completely abort seizures within 20 minutes and without recurrence during the following 40 minutes, followed by i.v. phenobarbital (58.2%), diazepam plus phenytoin (55.8%), and phenytoin alone (43.6%).[12] Another study (2008) comparing with i.v. valproic acid vs. i.v. phenytoin in treatment of SE and ARS, 49 with valproic acid and 25 phenytoin. In 43 (87.8%) of the valproic patients, the seizures discontinued, and no rescue medication was needed. Similar results were found in the phenytoin group in which seizures of 22 (88%) patients were well controlled. Side effects were found in 12% of the PHT group, and in none of the valproic group. Their conclusions are i.v. valproic seems to be effective and well tolerated in adult patients with SE or ARS.[13]

A recent randomized unblinded study that compared valproate to phenytoin in 68 patients found valproate to be superior at aborting SE as both a first-line (66% vs. 42%) and second-line (79% vs. 25%) agent.[14] There was a suggestion of a synergistic effect with other drugs when valproate was given as the second, third or fourth agent. The drug also has the advantage over phenytoin of better safety, serious side-effects being virtually unheard of in reports. Side-effects that have been reported in occasional patients include respiratory depression, tremor and transient disturbance of liver function tests. It may be given as a rapid intravenous infusion of up to 6 mg/kg/min to a maximum dose of 45 mg/kg, most reports using 20-30 mg/kg at a rate of about 3 mg/kg/min (approximately 2000 mg over 10 min for the average adult).

The prominent respiratory and cardiovascular side effects made diazepam taken over by lorazepam and midazolam. Same reasons made i.v. phenobarbital the last line in treating acute seizures. In a series of 38 patients with idiosyncratic side effects of phenytoin, the most common manifestations were rash, fever, lymphadenopathy, eosinophilia, abnormal liver function tests, blood dyscrasias, serum sickness, renal failure and polymyositis.[15] Symptoms usually occurred within 3 months after initiation of treatment. Other idiosyncratic reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, hepatitis, pseudolymphoma and lupus-like reaction. Iintravenous administered phenytoin can cause hypotension, atrial and ventricular conduction depression and ventricular fibrillation, especially in patients with preexisting diseases, advanced age and rapid infusion.[16] Thus, phenytoin should be used with caution and close cardiovascular monitoring when given intravenously.

Till recently, most currently available data of i.v. valproate were from adults. The published pediatric experience is scant. This made the study of Chang et al valuable, especially the patients were all Taiwanese children. Their study provides an experience that i.v. valproate is safe and efficacy in treating SE. But large-scale randomized comparative trials are warranted to further clarify the role of the drug in management of SE and ARS.

REFERENCES

1. Bourgeois BFD. Valproate. In: Wyllie E ed. The Treatment of Epilepsy, Principles and Practice. 3rd edition. Philadelphia: Lippincott Williams & Wilkins. 2001; 846-847.
2. Sugai K. Treatment of convulsive status epilepticus in infants and young children in Japan. Acta Neurol Scand 2007;186:62-70.
3. Hubert P, Parain D, Vallée L. Management of convulsive status epilepticus in infants and children. Rev Neurol (Paris) 2009;165:390-397.
4. Neville BGR, Chin RF, Scott RC. Clinical trial design in status epilepticus: problems and solutions. Epilepsia 2007;48:56-58.
5. Sofou K, Kristjánsdóttir R, Papachatzakis NE, Ahmadzadeh A, Uvebrant P. Management of prolonged seizures and status epilepticus in childhood: a systematic review. J Child Neurol 2009;24:918-926.
6. Arif H, Hirsch LJ. Treatment of status epilepticus. Semin Neurol 2008;28:342-354.

7. Campistol J, Fernandez A, Ortega J. Status epilepticus in children. Experience with intravenous valproate. Update of treatment guidelines. Rev Neurol 1999;29:359-365.
8. Yu KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status. Epilepticus and acute repetitive seizures. Epilepsia 2003; 44:724-726.
9. Uberall MA, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology 2000;54:2188-2189.
10. Trinka E. The use of valproate and new antiepileptic drugs in status epilepticus. Epilepsia 2007;48:49-51.
11. Glauser TA, Graves NM. Phenytoin and fosphenytoin. In: Wyllie E ed. The Treatment of Epilepsy, Principles and Practice. 3rd edition. Philadelphia, Lippincott Williams & Wilkins, 2001: 860.
12. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Eng J Med 1998;339:792-798.
13. Gilad R, Gilad R, Izkovitz N, Dabby R, Rapoport A, Sadeh M, Weller B, Lampl Y. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs. phenytoin. Acta Neurol Scand 2008;118:296-300.
14. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology 2006; 67:340-342.
15. Haruda F. Phenytoin hypersensitivity: 38 cases. Neurology 1979;29:1480-1485.
16. Mattson RH. Parenteral antiepileptic /anticonvulsant drugs. Neurology 1996;46:8-13.