

Management Of Epilepsy
Focus On Controlled Release Valproate

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Introduction

Epilepsy is a major health problem both in developed and developing nations. It has been estimated that nearly 1 in 20 individuals of the general population will have a seizure at some point in their lives, and that 1 in 200 will have recurrent seizures (epilepsy)¹. Epilepsy is defined as a condition characterized by recurrent (two or more) unprovoked seizures. Multiple seizures occurring in a 24-hour period are considered as a single seizure episode. A considerable number of patients who have suffered a single seizure have no further attacks, i.e. they do not develop epilepsy.

The situation with respect to the problem of epilepsy in India is complex due to several factors namely:

1. Paucity of epidemiological data (with respect of prevalence and incidence)
2. Large treatment gap due to ignorance and inadequacy of resources,
3. Patients' and relatives' perceptions regarding disease and expectations from therapy
4. Poor compliance of therapy and
5. Patients gravitating to irrational modes of therapy and quacks.

The care – giver (primary care doctor, physician, paediatrician and neurologist) is often faced with the question of selecting appropriate drug for optimum control of seizures. Fortunately, most first-line conventional drugs are available in India to have satisfactory blood levels of these drugs. Controlled-release preparations of carbamazepine and valproate have been recently introduced. Some newer drug like clobazam, lamotrigine, topiramate have been recently introduced.

This booklet introduces the concept of the use of controlled-release preparation for satisfactory results and better compliance in the control of seizures

Types of Epilepsy and The Role of Various Antiepileptic Drug (AEDs)

Antiepileptic drugs are the mainstay in the treatment of the disease. The search for newer and better drugs with minimal side effects is an ongoing process. The trend, till very recently, was to use phenobarbital, phenytoin, and primidone as primary agents. Of late, however, it is being increasingly realized that sodium valproate and carbamazepine are drugs of first preference. Sodium valproate is a broad spectrum anticonvulsant. It also has an edge over carbamazepine. Which has been reported to cause skin allergic reactions and sedation.

The following table (Table 1) illustrates various types of epilepsies and the drugs that are useful therein in order of preference.²

Type of Seizure	Preferred drugs
Generalized Seizures	
Tonic-Clonic Seizure	Carbamazepine
	Phenobarbital
	Phenytoin
	Primidone
	Valproate
Absence Seizure	Clonazepam
	Ethosuximide
	Valproate
Myoclonic seizure	Valproate
Partial seizures	
Simple Partial	Carbamazepine
Complex Partial	Phenytoin
Partial with Secondarily	Phenobarbital
Generalized tonic-clonic seizure	Primidone, Valproate

Table 1: Various types of epilepsies and the drugs useful therein (Adapted from Reference 2).

Focus on Controlled – Release Valproate

Composition

The controlled-release formulation of valproate contains sodium valproate and valproic acid in a ratio of 2:1. Sodium valproate is highly soluble in water whereas valproic acid is poorly soluble in water. When the two are combined in the formulation, it is possible to control the rate of dissolution and consequently the bioavailability of the active ingredients. This, in turn, results in sustained concentrations of valproate, eliminating very high peaks and troughs. The sustained level of valproate, while ensuring efficacy also improve the tolerability of the formulation. The ease of administration (i.e. once or twice daily) ensuring patient compliance.

Mechanism of action

Valproate has a broad spectrum of activity against both generalized and focal seizures. In addition, its simple structure of branched-chain fatty acid differs markedly from the substituted heterocyclic ring structure characteristic of older AED's.³

A number of hypotheses have been advanced to account for the anticonvulsant properties of vaproate.⁴ These suggestions include:

- Valproate increases the levels of the inhibitory neurotransmitter, gamma-butyric acid (GABA) at GABA_A and GABA_B receptors, possibly resulting from the activation of the synthetic enzyme glutamic acid decarboxylase and inhibition of the catabolic enzymes succinic semialdehyde dehydrogenase and GABA transaminase.
- Valproate potentiates post-synaptic responses to GABA.
- Valproate has a direct effect on neuronal membranes, e.g. affects potassium ion conductance.
- Valproate inhibits neurotransmission by the excitatory amino acids δ - hydroxybutyric acid, aspartic acid and glutamic acid.
- Valproate reduces dopamine turnover and increases levels of tryptophan and 5-HIAA in the brain.
- Valproate inhibits neuronal cell firing induced by NMDA.

Pharmacokinetic features

Valproate is completely absorbed following oral administration of the plain tablets, enteric-coated tablets or liquid preparations. Absorption may be delayed by the presence of food in the stomach. The extent of protein binding of valproic acid is usually about 90%, but the fraction bound is reduced as the total concentration of valproate is increased through the therapeutic range. Protein binding of valproic acid is decreased in geriatric patients, in patients with renal impairment and hepatic disease².

Valproic acid has an elimination half-life of 9 - 21 hours (average 12 - 13 hours)⁴. It is metabolized principally in the liver and its metabolites are excreted in urine.²

The steady-state pharmacokinetics of valproic acid 500 mg twice daily administered as controlled-release or enteric-coated tablet formulations were compared in 18 healthy volunteers. Lower $C_{m a x}$ (70.5 vs 93.5 mg/L) and higher minimum plasma drug concentrations (53.7 vs 41.4 mg/L) were observed with the controlled release tablet compared to the enteric coated tablet formulation, with no difference in the bioavailability between the two preparations⁵. In addition, the controlled-release tablet demonstrated less variations in peak-to-trough plasma drug concentrations (27% vs 72%) and did not show any delay in absorption or the absorption peak observed with the enteric coated tablet.⁵ **By producing more uniform plasma valproic acid concentrations, use of the controlled-release preparations may reduce the need for therapeutic drug monitoring and minimize the potential for concentration-dependent adverse effects.**

Clinical Efficacy of Sodium Valproate

Broad spectrum of activity

Several clinical trials have documented the efficacy and safety of sodium valproate in adults and children for the treatment of **generalized seizures (tonic-clonic, myoclonic and absences), partial seizures (simple and complex) and compound/combination seizures (including those refractory to treatment with other anti-epileptic drugs)**. Monotherapy with valproic acid has demonstrated efficacy equivalent to that of carbamazepine, phenytoin, and phenobarbital in the treatment of both generalized and partial seizures and ethosuximide in the treatment of absence seizures.⁵

Thus, comparative trials and extensive clinical experience have demonstrated the efficacy and tolerability of valproic acid and support its role as a valuable and well-established first-line treatment for patients with a broad range of seizure disorders.⁵

Controlled-Release Valproate – A Valuable Addition in Managing Epilepsy

The success of therapy depends on drug compliance. If the drug can be taken in a single or twice daily dose more patients are likely to take the drugs regularly. Besides such formulations may ensure steady plasma levels without significant fluctuations between peaks and trough levels. Controlled-release preparations of valproate, by virtue of providing sustained levels of valproate provide convenience to the patients and ensure their compliance.

Controlled-Released Valproate: Well Established Clinical Efficacy

A randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy of controlled-release valproate monotherapy by comparing seizure frequency in 143 patients with poorly controlled partial epilepsy resulted in mean reduction for secondarily generalized tonic clonic seizures of 70% in the high dose group (plasma level 80 to 150 mcg/mL) compared with 19% increase for those in the low dose group (25 to 50 mcg/mL). Adverse events that occurred more frequently in the high dose group included tremors, thrombocytopenia, alopecia, asthenia, diarrhea, vomiting, and anorexia. The study demonstrated the efficacy of valproate as monotherapy for the treatment of partial-onset seizures and supported its role as one of the first-line anti-epileptic drugs.⁶

Controlled-release formulations offer increased convenience to school children and ensure their compliance

In a study undertaken with a newly developed controlled-release formulation of valproate in children with epilepsy, the investigators studied plasma levels and behavioural effects in these children. Valproate plasma levels and performances in attention and vigilance tasks were monitored during a 12-h period (daytime), both during monotherapy of conventional valproate and 4 weeks after switching to a similar dosage of controlled-release preparations taken once daily. Neuropsychological assessment showed no significant differences, either between two formulations of valproate and no correlation was found between cognitive performance and valproate plasma levels. The authors concluded that the advantage of the controlled-release valproate is that the once daily regimen may increase compliance and is more convenient for school children.⁷

Tolerability Profile

Valproate is generally well tolerated and for this reason it is often preferred over other AEDs. Adverse effects associated with the drug are primarily gastrointestinal (nausea, vomiting, anorexia) in nature. The use of enteric-coated controlled-release formulations has minimized this. Weight gain, tremor and transient hair loss has been reported. It would be desirable to tell the relatives and the patients about the possibility of weight gain so that if required dietary adjustments may be made in advance. It has minimal neurological side effects

such as ataxia, sedation and impaired cognitive function a feature very important for epileptic patients. Other anti-epileptics like carbamazepine, or phenobarbital have these troublesome side effects. The incidence of hepatic effects can be minimized by avoiding administration to patients with high risk or with family history of liver disease.⁸

Controlled – Released Valproate Formulations Facilitate Easy Switchover

The question may be asked if patients on conventional three times a day valproate can be switched over to sustained-release (chrono) preparations given as a single dose. In a retrospective study, 113 patients were treated with a sustained-release form of valproate, known as the “chrono” formulation in most European countries. It was observed that patients treated with the old formulation of valproate could immediately receive the same daily dosage of the chrono-formulation without loss of seizure control when administered as a single evening dose. The tolerability of the chrono-formulation was good and twice or single daily dosing was preferred by the patients. Besides, the results of this study also showed that the efficacy of the chrono-formulation of valproate was comparable with that of other major anti-epileptic drugs such as carbamazepine. In refractory seizures, the combination of valproate chrono and carbamazepine seemed to be most satisfactory treatment.⁹

Use Of Sodium Valproate In Psychiatric Disorders

The significant role that GABA plays in mood and other psychiatric disorders has provided the rationale to examine sodium valproate in this regard. The drug has been evaluated in a range of psychiatric disorders such as mania, depression, anxiety, alcohol withdrawal and dependence, tardive dyskinesias, agitation associated with dementia and borderline personality disorder.¹⁰ The drug has shown promise in several disease states. The drug has been approved in the treatment of manic phase of bipolar disorder and for the prophylaxis of migraine.¹¹

Dosage

In Epilepsy

In addition to being the sole drug for treatment of epilepsy, sodium valproate can also serve as a part of polytherapy. For both these regimens the dose is 20 mg/kg body weight this can be increased up to a maximum of 2500 mg per day in adults and up to a maximum of 35mg/kg in children. Once the optimum dose is attained, the patient can be switched over to controlled-release sodium valproate. This serves to improve bioavailability of the drug and increases patient compliance.

The controlled release tablet of sodium valproate is not indicated in children with body weight of less than 20 kg because the formulation does not allow easy dose titration.

In the elderly, although the pharmacokinetics of sodium valproate is modified, they have limited clinical significance and dosage should be determined by seizure control.

Conclusions

Sodium valproate is a broad spectrum anti-epileptic drug-useful for generalized and partial onset seizures. The results in juvenile myoclonic seizures are spectacular. It is comparable in its efficacy to carbamazepine and phenytoin for partial onset seizures and is the favoured drug for generalized seizures and absence seizures. Favourable pharmacokinetic features and the tolerability profile are other scoring points in favour of sodium valproate – vis-à-vis other conventional AEDs. Its significant effects on GABA have led to investigation of potential uses in other psychiatric disorders. It has been approved for use in manic phase of bipolar disease.

The introduction of controlled-release formulations of valproate has added advantages. It offers the following benefits over conventional preparations of sodium valproate.

- Controlled release formulations of valproate provide more uniform levels of valproic acid, which, in turn, promote satisfactory control of seizures.
- Reduction in number of doses of controlled-release tablets of valproate (which can be given as single or twice daily doses) facilitates convenience and ensures compliance on the part of the patient.
- Controlled-release tablets of valproate minimize the requirement of therapeutic drug monitoring.

The controlled-release formulation of valproate may, therefore, be regarded as a refinement in anti-epileptic therapy and a useful choice for the treating doctors.

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