

# Verapamil as an Adjuvant Treatment for Drug-Resistant Epilepsy

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## Abstract

Almost one-third of the people suffering from epilepsy continue to have seizures in spite of using appropriate antiepileptics. Pharmacoresistance is defined as the failure to achieve seizure control with two or more anticonvulsant medications at appropriate daily dosage. Here, we discuss one such gentleman whose seizures had been intractable despite multiple antiepileptic drugs in maximum tolerable doses. Verapamil, a calcium channel blocker, was used for its P-glycoprotein inhibition properties to overcome the pharmacoresistance in this patient with satisfactory seizure control. There are a few studies with limited patients on the successful usage of verapamil in a patient with pharmacoresistant status epilepticus (SE). We intend to publish this case report to draw interest among the critical care physicians on pharmacoresistant SE, the different hypotheses that prevail, its causes and the available management strategies.

**Keywords:** P-glycoprotein, pharmacoresistance, status epilepticus

## INTRODUCTION

Among people with epilepsy, one-third continue to have seizures despite appropriate antiepileptics, resulting in considerable risk of psychosocial, cognitive dysfunction, and even death.<sup>[1-3]</sup> Furthermore, after the failure of two anti-epileptic drugs (AEDs), chances of seizure control using subsequent drug regimens has been less than ten percent.<sup>[4-6]</sup> Pharmacoresistance is defined as failure to achieve seizure control with first or second drug trial of an anticonvulsant at appropriate dosage.<sup>[7]</sup> About 26% of epilepsy is estimated to have drug resistance. Genetic predisposition, changes in drug targets in brain, failure of drugs to reach their targets and abnormal drug metabolism have a role in determining response to AEDs.<sup>[8,9]</sup>

This case report discusses a patient with intractable seizures despite multiple AEDs in maximum tolerable doses. Verapamil was used for its P-glycoprotein (P-gp) inhibition properties to overcome pharmacoresistance in this patient with satisfactory seizure control.

## CASE REPORT

A 71-year-old gentleman was referred to our hospital for embolization of multiple dural arteriovenous fistulas (AVF).

He was a diabetic and a hypertensive managed with insulin, metoprolol, and olmesartan. He was on levodopa/carbidopa and amantadine for rigidity and tremors. He also had a history of cerebral vein thrombosis for 2 years, and he was on anticoagulants. He was managed by a neurologist for 4 months before this admission for recurrent seizures and progressive decline in cognitive functions with multiple AEDs. On admission, he was on phenytoin 400 mg/day, sodium valproate 1400 mg/day, and carbamazepine 1200 mg/day.

On evaluation for recurrent complex partial seizures and rapidly declining cognitive functions, magnetic resonance imaging of the brain revealed multiple dural AVF. Digital subtraction angiography confirmed multiple dural AVF involving superior sagittal sinus and transverse sinus with severe venous hypertension.

While awaiting definitive procedure for AVF, he developed status epilepticus (SE) despite continuing his three AEDs.

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Midazolam infusion was initiated at 0.1 mg/kg/h, carbamazepine dose could not be escalated due to hyponatremia. Later, sodium valproate was withheld due to hyperammonemia.

Electrical SE persisted despite 24 h of midazolam infusion at 0.2 mg/kg/h and thiopentone infusions at 5 mg/kg/h. Dyselectrolytemias were addressed. Serum AED levels were found to be subtherapeutic despite maximum tolerable doses as shown in Table 1.

Possible causes for pharmacoresistance were evaluated. Awaiting repeat AED levels, Verapamil 40 mg every 8 h was initiated for P-gp inhibition effect. Convulsions stopped within 12 h of initiation of verapamil and patient remained seizure free since then. AED levels sent just before initiation of verapamil (5 days after withdrawing valproate) continued to be subtherapeutic as shown in Table 2. On day seven, he underwent squid embolization of multiple dural AVF and venoplasty with stenting. Postprocedure patient remained seizure free; his mentation improved and was discharged on day 11.

## DISCUSSION

One-third of the patients with epilepsy remain drug resistant despite the development of more than ten new AEDs in the past decade. Approximately 60% of patients with focal epilepsy and 20% with primary generalized epilepsy develop drug resistance during their course. People with pharmacoresistant epilepsy have up to 10 times more likelihood of dying compared to normal population.<sup>[10]</sup> A study conducted in the United States (US) in 1990s estimated that the annual cost of refractory epilepsy in adults exceeds US dollars 11,745 per person and would definitely be more now.<sup>[11]</sup> Another study found that costs correlate with severity of illness and that the cost of treating a patient with resistant epilepsy is eight times higher.<sup>[12]</sup>

The current definition for pharmacoresistant epilepsy would be failure to control seizures despite trial of two or more suitable drugs at maximum tolerated doses. Common causes of treatment failure such as poor compliance and inappropriate selection of first-line AEDs should be addressed at the earliest.

**Table 1: Serum drug levels (by chemiluminescence assay)**

| Serum drug levels | Patient value (mcg/ml) | Therapeutic range (mcg/ml) |
|-------------------|------------------------|----------------------------|
| Phenytoin         | 3.67                   | 10-20                      |
| Carbamazepine     | 3.08                   | 4-10                       |
| Valproic acid     | 2.7                    | 50-100                     |

**Table 2: Serum drug levels after withdrawing Valproate**

| Serum drug levels | Patient value (mcg/ml) | Therapeutic range (mcg/ml) |
|-------------------|------------------------|----------------------------|
| Phenytoin         | 1.77                   | 10-20                      |
| Carbamazepine     | 9.12                   | 4-10                       |
| Valproic acid     | 17.3                   | 50-100                     |

It is equally important to identify false pharmacoresistance, caused by incorrect drug selection or dosage, wrong diagnosis, and improper assessment of drug response. Multidrug resistance is insensitivity to a broad spectrum of drugs acting on different receptors and by different mechanisms.<sup>[13]</sup>

Variation in response to AEDs can be due to factors related to disease, drugs, or patient. Factors related to disease include etiology, seizure progression causing alteration of drug targets (pharmacodynamics hypothesis) and altered uptake of drug into brain (transporter hypothesis). Factors related to drug include the development of tolerance, lack of anti-epileptogenic action rather than suppressing spread of epileptic potentials, and paucity of drugs with specific action to control seizures.

Multidrug resistance efflux transporter proteins (MDPs) play a major role in maintaining appropriate AED levels through their presence in the blood-brain barrier. Among the MDPs, the P-gp, also known as adenosine triphosphate binding cassette sub-family B-member1 or multidrug resistance protein 1, is a drug efflux transporter that limits the access of numerous AEDs to their site of action in the brain. Many studies were done on inhibition of P-gp and decreasing it is over expression in the management of pharmacoresistant epilepsy.

A functional role for P-gp in pharmacoresistance has been experimentally demonstrated in many studies showing that upregulation of P-gp is associated with reduced brain penetration of AEDs.<sup>[13-15]</sup> There exists a correlation between P-gp expression rates and pharmacosensitivity.<sup>[16]</sup>

Verapamil, a phenylalkylamine calcium channel blocker, can also inhibit P-gp at blood-brain barrier, has been used with encouraging results in drug-resistant epilepsy syndromes.<sup>[7]</sup> The main hypotheses are that verapamil may increase the brain influx of AEDs by blocking P-gp. It also maintains the resting membrane potential by modulating the abnormal calcium influxes in neurons, which are considered to be responsible for membrane hyper-excitability, yielding seizure disorders.<sup>[17]</sup>

Our patient who was on maximum tolerated dose of multiple AEDs continued to have seizures. Addition of verapamil controlled the frequency of seizures without adding any other antiepileptic to his regimen. There are only few studies with limited patients reporting successful treatment of refractory SE with verapamil.<sup>[18-20]</sup>

## CONCLUSION

Proper look out for etiology, drug interactions, appropriate dosing of anti-epileptic should be considered early in the management of seizures. Failure of two or more anti-epileptic drug trials should prompt early evaluation of the risk factors for pharmacoresistance. Novel approaches including nonpharmacological and other pharmacological approaches should be considered in the management of drug-resistant seizures. Verapamil as an add-on treatment should be considered in drug-resistant epilepsy.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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