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Efficacy of verapamil as an adjunctive treatment in children with drug-resistant epilepsy: A pilot study

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ABSTRACT

Purpose: Verapamil, a voltage-gated calcium channel blocker, has been occasionally reported to have some effect on reducing seizure frequency in drug-resistant epilepsy or status epilepticus. We aimed to investigate the efficacy of verapamil as add-on treatment in children with drug-resistant epilepsy.
Methods: Seven children with drug-resistant structural-metabolic, unknown or genetic (*e.g.*, Dravet syndrome [DS]) epilepsy received verapamil as an add-on drug to baseline antiepileptic therapy. Verapamil was slowly introduced at the dosage of 1 mg/kg/day and titrated up to 1.5 mg/kg/day. After completing the titration period, patients entered a 14-month maintenance period and were followed up at 3, 8, and 14 months. Heart monitoring was performed at baseline and at each follow-up. The primary outcome measure was the response of seizures to verapamil.
Results: Three subjects with genetically determined DS showed a partial (reduction of 50–99%) response for all types of seizures. A patient with DS without known mutation showed a partial control of all types of seizures in the first 13 months; then seizures worsened and verapamil was suspended. Two patients with structural epilepsy and one with Lennox–Gastaut syndrome showed no improvement. Any side effects were recorded.
Conclusions: Add-on treatment with verapamil seems to have some effect in controlling seizures in patients with genetically determined DS. Our observations justify further research on the relationship between calcium channels, calcium channel blockers, and channelopathies.

1. Introduction

Resistance to antiepileptic drugs (AEDs) is one of the most common unsolved issues in the treatment of paediatric- and adult-onset epilepsy. It is estimated that up to 26% of epilepsy can show drug resistance, thus leading to neuropsychiatric and social impairment, lower quality of life, greater morbidity, and a higher risk of death.[1,2] Although several new AEDs have been developed in the recent years, epilepsy remains resistant to drug therapy in about one-third of patients, thus encouraging the discovery of drugs that act on the mechanisms underlying pharmacoresistance. Genetic predisposition, abnormal drug metabolism, the failure of drugs to reach their targets, and changes in drug targets in the brain have all been considered to be involved in determining response to AEDs.[3]

Multidrug transporters (MDTs) are likely to play a role in the pathogenesis of drug resistance in epilepsy, acting at the level of the blood–brain barrier (BBB) by returning AEDs to the blood vessels and lowering brain penetration and concentration.[4,5] Among the MDTs, the P-glycoprotein (Pgp), also known as ATP-binding cassette sub-family B member 1 (ABCB1) or multidrug resistance protein 1 (MDR1), is a drug efflux transporter that limits the access of numerous AEDs to their site of action in the brain.[6,7] Verapamil, a voltage-gated calcium channel blocker that can also inhibit Pgp at the BBB level, has been used with encouraging results in epileptic patients suffering from drug-resistant epilepsy syndromes[8] or status epilepticus.[9–12] The main hypotheses on this topic are that verapamil may increase the brain influx of AEDs by blocking Pgp and may also maintain resting membrane potentials by modulating the abnormal calcium influxes in neurons, which are considered to be responsible for membrane hyper-excitability, yielding seizure disorders.[8] The aim of this

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study was to investigate the efficacy of add-on verapamil treatment in a group of children with drug-resistant epilepsy.

2. Methods

Seven patients with structural-metabolic (two), unknown (two), or genetic (three) drug-resistant epilepsy were recruited in a prospective, add-on, open-label study from the Paediatric Neurology Unit of Sapienza University of Rome, Italy and an epilepsy centre of Dianalund, Denmark. All selected patients had the following features: (1) drug-resistant epilepsy despite the use of three previous AEDs, alone or in combination; (2) the use of at least two AEDs, but no more than four; (3) more than three seizures per month in the last 6 months; and (4) written informed consent from parents and/or caregivers, and their complete helpfulness in administering the study drug according to the provided schedule. Parents/caregivers were comprehensively informed about the possible adverse events of verapamil, and were educated to immediately refer to us in case of any side effect. They were also asked to correctly complete a diary recording the frequency, type, and duration of seizures. Seizures and epilepsy aetiology were classified according to ILAE terminology.[13]

The study comprised the following phases:

1. *Baseline phase*. Past medical history was carefully collected; all the patients underwent full neurological examination, brain magnetic resonance imaging (MRI), and video-electroencephalogram (EEG) recording. Heart monitoring (*i.e.*, blood pressure, electrocardiogram [ECG], and paediatric cardiologist evaluation) and blood examinations (*i.e.*, routine blood cell counts and biochemistry, AED level) were undertaken for each patient.
2. *Titration phase*. In all children, verapamil was slowly introduced at the dosage of 1 mg/kg/day and titrated up to 1.5 mg/kg/day in a period of 14 days. Verapamil was administered not later than 6 p.m. in order to avoid physiological bradycardia. We kept in mind that if baseline therapy comprised phenobarbital or phenytoin, blood verapamil levels could be reduced due to enzymatic induction, and that verapamil could increase blood levels of carbamazepine. Patients were followed up weekly during the titration phase.
3. *Follow-up phase*. After completing the titration period, patients entered a 14-month maintenance period and were followed up at 3, 8, and 14 months, if no adverse effects or complications occurred. In case of side effects, complication, or worsening of seizure, treatment with verapamil was promptly suspended. At each follow-up, patients underwent physical and neurological examination, ECG, blood chemistry, AED dosages, and EEG.

The primary outcome measure was the response of seizures to verapamil. It was classified as 'seizure freedom' in case of seizure disappearance (100% responders), 'partial response' if the reduction was 50–99%, 'no response' if seizure reduction was $<$50%, and 'seizure worsening' if seizure frequency and/or severity increased. We also evaluated interictal EEG changes (improved, worsened, or unmodified interictal epileptic activity). Safety was evaluated by recording every type of adverse event, taking into consideration that the most important side effects relating to verapamil are headache, arterial hypotension, vertigo, constipation, itch sensation, and kidney or liver failure.

3. Results

The main patient data are summarised in Table 1. Seven patients (three males, four females; age range: 4.2–18 years; mean age: 11 years) were enrolled in this study. Two patients (1 and 2, Table 1) have been previously reported.[8] Four cases had a diagnosis of the Dravet syndrome (DS) spectrum, including one severe myoclonic epilepsy of infancy (SMEI) patient (patient 1, Table 1) without mutation of the sodium channel alpha-1 subunit (SCN1A) and three SMEI patients (2–4) with mutation of the SCN1A. One patient (number 5) had a diagnosis of Lennox–Gastaut syndrome (LGS); SCN1A analysis did not reveal anomaly in this patient. In two cases, the diagnosis of symptomatic epilepsy was achieved, including a case (patient 6) of semilobar holoprosencephaly with agenesis of the corpus callosum and a case (patient 7) of periventricular leukomalacia with diffuse cortical atrophy as a consequence of hypoxic-ischaemic encephalopathy.

Seizure semiology was classified as myoclonic in six patients, febrile in four patients, generalised tonic-clonic, atypical absence, and atonic in three patients, reflex, generalised tonic, simple partial, hemiclonic, and complex partial with secondary generalisation in two patients, and gelastic in one patient; four patients had experienced status epilepticus. All of the patients showed more than one type of seizure, with at least four different semiologies for each subject. At baseline, all patients presented with daily (1–10) seizures and received at least two other AEDs, used in various combinations according to the type of epilepsy. Moderate-to-severe developmental delay was present in all the subjects.

Blood examinations obtained during verapamil administration revealed normal results for erythrocyte and leukocyte counts, amylase, transaminases, gamma-glutamyl transpeptidase, and blood urea nitrogen. Verapamil did not alter the blood levels of the associated AEDs, except for a slight increase (20% from baseline blood level) of phenytoin level in one case (patient 1). No interactions with other drugs (*e.g.*, antipyretics, antibiotics) or any side effects were recorded.

The patient with DS without mutation of the SCN1A or protocadherin 19 (PCDH19) gene showed a partial control of all types of seizures in the first 13 months; then seizures worsened and verapamil was tapered and suspended. The three subjects with DS and SCN1A mutation showed a partial response for all types of seizures; additionally, an improvement in cognitive performances (such as attention, concentration, participation, and socialisation) was reported by parents (and verified by us during each follow-up), but we did not verify it with appropriate tests. A partial control of generalised tonic-clonic seizures was observed in the boy with LGS for a brief period; however, seizures quickly returned at the baseline frequency. Finally, patients with symptomatic epilepsy showed no effects or a brief improvement with subsequent worsening, after which verapamil administration was suspended. Improvement in interictal epileptic activity on EEG was clearly observed only in one case (patient 2): it consisted of an almost complete disappearance of diffuse spikes and spike-and-wave complexes during sleep and wakefulness, with rare spikes in the right frontotemporal region.

4. Discussion

We report here on seven children with drug-resistant epilepsy who received verapamil as add-on therapy, with the goal of reducing seizures by an inhibition of Pgp function at the level of the BBB, in order to improve the brain inflow of AEDs. Experimental studies in animal models suggested this strategy.[14,15] The Pgp is a MDT that acts at the level of the BBB and is postulated to be involved in the pathogenesis of drug resistance in epileptic subjects by sending the AEDs back in the lumen of brain vessels, forbidding their influx and action.[16,17] Several AEDs, or their metabolites, are known to be substrates of the Pgp (*i.e.*, carbamazepine-epoxide, felbamate, gabapentin, lamotrigine, levetiracetam, phenytoin, phenobarbital, and topiramate).[5,6] The hypothesis that the Pgp may be involved in mechanisms of drug resistance is derived from investigations in rodent models and