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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

Table 1
Main features of the reported patients.

Patient (age, sex)	Epilepsy type	Genetic analysis	Seizure type and frequency (before verapamil)	Developmental delay	Brain MRI	Seizure (under verapamil)	Inter-ictal EEG (under verapamil)	Cognitive function (under verapamil)	Side effects	AEDs associated with verapamil
1 (14 years, F)	DS	SCN1A and PCDH19 negative	FS (at onset); RS and M (25–30 daily); PS (monthly); GTCS and SE (bimonthly)	Moderate	N	Partial control of all types of seizures in the first 13 months (reduction of 90%); then worsening and suspension	Unmodified	No effects	No	VPA, TPM[c], PHT[c], ETS
2 (8 years, F)	DS	SCN1A mutation c.716C>T	FS (at onset); M (15–20 daily); GCTS, PS and SE (monthly)	Severe	N	Partial control of M, GTCS, PS (90%). Disappearance of SE	Improvement	Improvement[a]	No	PB[c], LTG[c], TPM[c]
3 (4 years 2 months, M)[b]	DS	SCN1A mutation c.3972insT	FS (at onset); H (2 per month), At and MA (60–100 daily)	Moderate	N	Partial control of all types of seizures (reduction of 60%)	Unmodified	Improvement[a]	No	LEV[c], VPA
4 (4 years 2 months, M)[b]	DS	SCN1A mutation c.3972insT	FS (at onset), H (1 monthly), At and MA (100–150 daily)	Moderate	N	Partial control of all types of seizures (reduction of 60%)	Unmodified	Improvement[a]	No	LEV[c], VPA
5 (18, M)	LGS	SCN1A negative	T (1–2 daily); At and A (8–10 weekly); GTCS (2–4 monthly)	Severe	N	Partial control of GTCS in the first 2 months (0–1 monthly); then return at baseline	Unmodified	No effects	No	LEV[c], VPA
6 (15 years, F)	Symptomatic epilepsy	None performed	M and RS (6–7 daily); CPS with SG and T (1–2 monthly)	Severe	Periventricular leukomalacia and diffuse cortical atrophy	No effects	Unmodified	No effects	No	ZNS, LTG[c], CLZ
7 (14 years, F)	Symptomatic epilepsy	None performed	M (8–10 daily); CPS with SG (2–3 per month); T and G (monthly)	Severe	Semilobar					holoprosencephaly; corpus callosum agenesis
Partial control of M in the first 3 months (0–3 daily); then worsening of all seizures and suspension	Unmodified	No effects	No	LCS, LTG[c], PB[c]						

List of abbreviations: DS, Dravet syndrome; SCN1A, sodium channel alpha-1 subunit; PCDH19, protocadherin 19; GTCS, generalised tonic clonic seizures; M, myoclonic seizures; H, hemiclonic seizure; MA, myoclonic-atonic seizure; PS, partial seizure; T, tonic seizures; G, gelastic seizures; RS, reflex seizures; SE, status epilepticus; At, atonic seizures; A, atypical absence seizures; CPS, complex partial seizure; SG, secondarily generalisation; N, normal; VPA, valproic acid; PB, phenobarbital; LTG, lamotrigine; TPM, topiramate; LEV, levetiracetam; PHT, phenytoin; ETS, etosuximide; ZNS, zonisamide; LCS, lacosamide; CLZ, clobazam.

[a] Improvement of cognitive functions consisted of higher attention, concentration, participation and socialisation for all the children.

[b] Patients 3 and 4 are a couple of identical twins.

[c] AEDs that are known to be substrate of Pgp.

human brain tissue.[17] Drug-resistant rats have enhanced endothelial Pgp expression in limbic regions ipsilateral to the epileptic focus compared with drug-responsive rats[18]; post-surgery or post-mortem tissues of pharmacoresistant patients have revealed that chronic epilepsy is associated with inflammation and enhanced Pgp (without affecting other transporters) at the BBB level.[19,20] This overexpression leads to a reduced brain concentration of Pgp substrates,[15] which can be restored after Pgp inhibition.[14] Furthermore, it has been demonstrated that seizure activity can transiently increase Pgp expression in brain capillary endothelial cells of epileptic dogs.[21] However, a recent study of idiopathic drug-resistant canine epilepsy failed to demonstrate the efficacy of verapamil add-on treatment in improving seizure control and increasing phenobarbital concentration in the cerebrospinal fluid; verapamil treatment was discontinued in all the dogs due to side effects (*e.g.*, bradycardia and arterial hypotension) or an increase in seizure frequency.[16]

Studies on humans are limited to a few case reports. Firstly, Summers and colleagues described successful treatment with verapamil in a 24-year-old woman with idiopathic intractable complex partial seizures.[9] Successively, some of us used verapamil in a case of refractory status epilepticus and supra-ventricular tachycardia[10] and in two patients with SMEI (patients 1 and 2 in Table 1).[8] Schmitt et al. reported on a 20-year-old woman with idiopathic frontal lobe epilepsy and recurrent status epilepticus, and Pirker and Baumgartner described a case of structural focal status epilepticus: both patients showed a favourable response to add-on treatment with verapamil, with the cessation of status epilepticus.[11,12] Recently, the relationship between pharmacoresistance and Pgp overexpression has been assessed *in vivo* for the first time, by using positron emission tomography (PET) with the Pgp substrate (R)-[^{11}C]verapamil in patients with temporal lobe epilepsy.[22] Previously, other authors failed to detect statistically significant differences by using the same technique.[23] Feldmann and colleagues discovered reduced uptake of Pgp substrate in the temporal lobe of drug-resistant patients (*i.e.*, indicating a higher Pgp baseline activity) compared with seizure-free subjects, and attenuated increase of substrate after Pgp inhibition by means of tariquidar in treatment-resistant patients compared with healthy controls. This *in vivo* result was confirmed by *ex vivo* Pgp measurement in temporal lobe tissues of five patients who underwent surgery.[22]

In this add-on open-label study, all the reported patients received common AEDs in various combinations according to clinical features; each patient received at least one AED that is known to be a substrate of Pgp at the level of the BBB (see Table 1).[6–9] Cardiac side effects of verapamil were not observed in this study; side effects limited long-lasting treatment in previous studies in humans and animal models.[10,16] Treatment with verapamil gave encouraging results in patients with DS but not in patients with LGS or structural epilepsy. In one case of SCN1A- and PCDH19-negative DS, improvement in myoclonic, partial, and generalised seizures was limited to a period of 13 months, when seizures worsened and verapamil was discontinued.[8] At present, this girl, still followed-up in our centre, is under therapy with multiple AEDs, and her seizures remain drug-resistant. Patients with genetically confirmed DS showed a favourable response in terms of control of seizures and cognitive performances, although a standardised scale was not used for measuring improvements in behaviour. Notably, these three subjects differ from case 1 in the presence of a mutation in the SCN1A, which is known to be responsible for 80% of DS.

DS is a drug-resistant epileptic encephalopathy characterised by recurrent and long-lasting febrile seizures, afebrile seizures (*e.g.*, myoclonic, complex partial, and atypical absence), the regression of cognitive function, ataxia, and pyramidal signs.[24] It has been shown that both gain- and loss-of-function SCN1A mutations may alter the neuronal Na^+ current and brain excitability, resulting in a final phenotype that is DS.[25]

It is known that neuronal membrane equilibrium is the result of different ion flows (sodium, potassium, and calcium) that contribute to the maintenance of the state of membrane polarisation and neuronal excitability.[26,27] In our previous work, we speculated that verapamil may also act by: (a) diminishing Ca^{++} entry into the cell; (b) activating potassium–calcium channel sensitive with direct binding of intracellular Ca^{++}; and (c) counteracting the action of persisting current induced by non-functional SCN1A *via* the diminution of intracellular Ca^{++} with final membrane repolarisation.[7] In other words, verapamil, beside its effect on Pgp activity, may also be effective in restoring ionic membrane equilibrium.

Our good results in terms of seizure control in patients with DS and SCN1A mutations might be related to these actions. In contrast, the improvement in seizure control with subsequent worsening in the patient with DS without SCN1A anomaly and with LGS might only depend on temporary inhibition of the Pgp, as we previously speculated.[8] Furthermore, we cannot exclude that the partial or negative results observed in these two patients, as in the subjects affected by structural epilepsy, might be related to unknown (drug-resistant) epilepsy-causing mechanisms different from Pgp action or Ca^{++} flows towards cellular membranes.[3] Unfortunately, we did not quantify the impact of Pgp on the drug resistance observed in our patients (*in vivo*, by performing a PET scan with the Pgp substrate (R)-[^{11}C]verapamil before [and after] the treatment with verapamil, and *ex vivo* by analysing the ATP binding cassette 1 (*ABC1*) gene C3435T polymorphism[28] or studying the Pgp in surgical tissues). To answer the many questions on the relationship between Pgp expression and antiepileptic drug resistance[29] is beyond the aims of this study.

In conclusion, treatment with verapamil seems to have some effect in controlling seizures in patients with DS and SCN1A mutations, while it was less effective in patients with DS without SCN1A mutations and LGS. No effect was noticed in patients with structural epilepsy. Inhibition of the Pgp and restoring of neuronal membrane ion equilibrium might explain the effectiveness of verapamil in treating SCN1A-mutated DS patients. The main limits of this study are the small number of enrolled subjects, which did not allow statistical analysis, and the lack of a blinded and placebo-controlled design. Our observations justify further research on the relationship between calcium channels, calcium channel blockers, and channelopathies. The recent application of PET with the Pgp substrate (R)-[^{11}C]verapamil will be useful for novel combined imaging and pharmacological trials in epileptic treatment-resistant patients.

Conflict of interest statement

None of the authors have any conflict of interest to disclose. None of the authors received financial sources for this study.

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