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A pilot double-blind trial using verapamil as adjuvant therapy for refractory seizures

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CYP enzymes

Summary
Rationale: Given verapamil's property as a glycoprotein inhibitor, this drug could increase the effective concentration of antiepileptic drugs (AEDs) in the epileptic foci, reducing the number of seizures. This pilot study was designed to evaluate the safety and efficacy of verapamil as adjunct therapy in pharmacoresistant patients with focal onset seizures.
Methods: This was a single-centered, randomized, double-blind and placebo-controlled trial evaluating verapamil as an add-on therapy for adult patients with refractory epilepsy.
Results: Twenty-two patients were randomized, but five of them withdrew and one patient passed away after consent, having no exposure to either verapamil or placebo; four patients withdrew during or after the double-blind phase due to side effects. From these four patients, only one patient was in the verapamil group. Twelve patients (59%) finished the study. Some patients experienced lower seizure frequencies, but none of them reached 50% reduction. In addition, there was no statistically significant decrease in the seizure frequency of patients receiving verapamil. When comparing the verapamil with the placebo at the double-blind or the open label study phases, the average difference in seizure range also failed to show significance ($p = 0.41$ and $p = 0.98$, respectively). No significant cardiovascular effects were observed, and side effects unique to verapamil were skin rashes and feet edema. Throughout the study, carbamazepine, valproic acid and clobazam levels increased following verapamil intake; minor dosage adjustment was required in one patient on carbamazepine.

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Conclusions: This pilot study has shown mild benefits of verapamil use in comparison to placebo as an add-on therapy for a group of non-selected patients with refractory epilepsy. A partial response in a subset of patients was seen. No significant safety problems happened, but adjustments on AEDs may be required during verapamil use.

Introduction

Despite the emergence of several novel antiepileptic drugs (AEDs) over the last years, refractoriness is still a problem amongst epilepsy patients. Epidemiological data has shown that between 30% and 40% of patients will present with poorly controlled seizures despite AEDs treatment (Kwan and Sander, 2004). The management of refractory epilepsies is still a challenge, as not all the mechanisms of pharmacoresistance are fully understood. Moreover, head-to-head trials with new AEDs rarely demonstrate superiority of one drug over others (French, 2007; French and Gazzola, 2013). In fact, the percentage of refractory patients who have achieved a 50% reduction in seizures using new AEDs as an adjunctive therapy is still <40%, despite these drugs acting through different mechanisms (French, 2007; French and Gazzola, 2013; Barcs et al., 2000; Cereghino et al., 2000; Cramer, 1999; Faught et al., 2001).

One postulated mechanism of AED resistance is the over-expression of P-glycoprotein (P-gp) in the blood brain barrier of epileptic foci (Kwan and Brodie, 2005; Löscher and Potschka, 2005; Schmidt and Löscher, 2005; Sisodiya et al., 2002). Experimental studies have suggested that multidrug transporters such as P-gp play an important role in epilepsy pharmacoresistance by regulating the efflux of AEDs through the blood—brain barrier (BBB) back into blood vessels (Potschka and Löscher, 2001; Siddiqui et al., 2003). Therefore, the overexpression of P-gp on epileptic foci may account for inadequate levels of AEDs where they are most needed. The calcium (Ca^{2+}) channel blocker verapamil, is a well-known non-selective P-gp inhibitor that could reduce the efflux of AEDs from the brain, and consequently increase the effective concentration of AEDs in the epileptic foci (Potschka and Löscher, 2001; Potschka et al., 2002). Furthermore, verapamil inhibits cytochrome p450 (CYP450), which may increase serum AEDs concentrations, and consequently the efficacy and/or toxicity, of drugs such as carbamazepine (Macphee et al., 1986; Summers et al., 2004).

In non-controlled open label studies and case reports, verapamil has been reported as a potential antiepileptic adjunctive therapy for (i) isolated patients in status epilepticus (Summers et al., 2004; Iannetti et al., 2005; Pirker and Baumgartner, 2011; Schmitt et al., 2010); (ii) patients with severe myoclonic epilepsy of infancy (SMEI) (Iannetti et al., 2009; Wical and Wandorf, 2013), and (iii) patients with focal onset seizures, particularly those with temporal lobe epilepsy (TLE) (Asadi-Pooya et al., 2013). However, presently there still have not been any placebo controlled clinical trials conducted to support verapamil's efficacy as an adjuvant antiepileptic treatment.

The goal of this study was to prospectively evaluate the safety and efficacy of verapamil versus placebo as an adjunct therapy for focal seizures in refractory epilepsy patients on standard AED therapy.

Materials and methods

Patients

Inclusion criteria: (1) patient eligibility for this study was limited to men and non-pregnant women with refractory epilepsy, aged 18—65 y-old. (2) Baseline seizure activity: at least four focal seizures and seizure-free interval no longer than four weeks during the baseline study phase; (3) patients should be on at least one AED that is a substrate for P-gp such as carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LTG), valproic acid (VPA), phenobarbital (PB), primidone (PRM), gabapentin (GBP), levetiracetam (LEV) or tompiramate (TPM) (Kwan and Brodie, 2005; Löscher and Potschka, 2005; Schmidt and Löscher, 2005; Sisodiya et al., 2002; Schmitt et al., 2010; Majkowski et al., 2005); and (4) ability of patients or caregivers to keep a seizure diary throughout the entire study.

Exclusion criteria: pregnant women, patients with seizures of metabolic, neoplastic or infective origin, major psychiatric disorders, psychogenic non-epileptic seizures, serious medically unstable diseases, verapamil intolerance or contraindication, and subjects currently receiving verapamil or other antihypertensive medications. All study candidates were evaluated by a cardiologist before entering the study.

Clinical information regarding patient's age, sex, etiology and duration of epilepsy, seizure frequency at baseline and number of concomitant AEDs was gathered.

The protocol as well as the consent forms was approved by the Research Ethics Board of the University Health Network.

This study was registered in the NIH clinical trials website with number: NCT01126307.

Design

This pilot study was a single-centered, randomized, double-blind and placebo-controlled adjunctive therapy trial that evaluated verapamil 240 mg daily versus placebo. The trial consisted of three phases: an eight-week baseline phase, a 16-week double-blind treatment phase, and a 12-week open-label treatment extension phase. In the eight-week baseline phase of the study before randomization, each patient underwent a physical, cardiological and neurological examination, an echocardiogram, 24-h cardiac Holter monitoring, as well as laboratory analyses for AED levels, hematologic screening and liver function. During the study, patients were maintained on the same doses of their

original AEDs, except for minor dose adjustments (see below). Plasma concentration of at least one AED had to be within the therapeutic range. If no therapeutic range was defined for the AED, the dosage was not to exceed the maximum recommended dose. Patients were randomized into the two different groups, by chance, assigned by the clinical trials pharmacist, having an equal opportunity of receiving either treatment. Clinical staff and patients did not know which treatment they were receiving in the double-blind phase.

In the double-blind treatment phase, patients were instructed to initially take either 80 mg of verapamil or placebo once daily for one week, then twice daily during the second week, and finally 80 mg three times daily from the third week until the end of double-blind treatment phase. During every visit after the baseline, patients underwent a physical and neurological examination as well as drug level analysis. The open-label extension phase consisted of 12 weeks in which all patients received 240 mg of verapamil daily. Patients on the placebo group were titrated as follows: 80 mg of verapamil once daily for one week, then twice daily during the second week, and finally 80 mg three times daily from the third week until the end of open-label treatment phase.

Efficacy

The primary end-point to assess efficacy was the percent reduction in seizure frequency per week during the double-blind phase relative to baseline in patients receiving verapamil compared to those receiving placebo. Seizure frequency per week was defined by the total focal onset seizure count in the phase divided by the number of weeks in each phase. The definition of treatment efficacy used was a $\geq$50% reduction in the number of seizures (per week during the double-blind treatment phase relative to the baseline).

Safety and side effects

AED trough levels were determined once during baseline, in the five visits of the double-blind treatment phase, and in the four visits of the open-label treatment extension phase. All side effects reported by patients in the double-blind and the open-label treatment phases were recorded. If clinical signs of toxicity due to interactions between verapamil and AEDs occurred, the dosages of AEDs were decreased until side effects subsided. Patients underwent 24-h cardiac Holter monitoring and echocardiogram once during baseline, and the Holter monitoring was repeated after the open-label phase for those who completed the study.

Statistical analysis

A non-parametric Friedman two-way ANOVA test with Bonferroni post hoc correction for multiple comparisons was used to examine the differences in seizure frequency between patients on verapamil or placebo at baseline, double blind, and open label phases of the study. Baseline seizure frequency was set to 100% for each individual with double-blind and open-label seizure frequencies normalized to this value. Significance was set at $p < 0.05$.

Results

Patient accounting and characteristics

Twenty-two patients were initially randomized for this study. However, five of them withdrew soon after consent having no exposure to either verapamil or placebo. One patient died after consent but before verapamil exposure due to sudden unexpected death in epilepsy.

Four patients withdrew during ($n = 1$) or after ($n = 3$) the double-blind phase due to side effects. From these four patients, only one patient was in the verapamil group (see side effects).

Twelve patients (59%) completed the study. Their clinical characteristics are summarized in Table 1.

Efficacy of verapamil as an add-on therapy for seizures

Analysis of the average frequency of seizures between verapamil and placebo groups throughout the various study phases failed to reveal any significant differences (Table 1). The average seizure frequency of the seven patients in the verapamil group did not significantly change from baseline (set at 100%) to either the double-blind ($104.8 \pm 11.9\%$; $p = 0.86$) or open-label ($106.8 \pm 17.3\%$; $p = 0.80$) phases (Fig. 1). Similarly, there were no significant differences

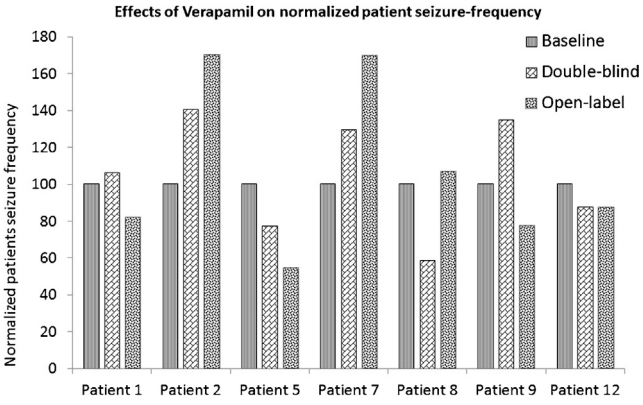

Figure 1 Effects of verapamil on normalized patient seizure-frequency. Histogram showing the normalized patient seizure frequency in the verapamil group during baseline, double-blind, and open-label study phases. Baseline seizure frequency was set to 100% for each individual patient with double-blind and open-label seizure frequencies normalized and compared with this value. Lower seizure frequency during the double-blind study phase was seen in the patients 5, 8 and 12. Albeit patient 8 had an initial seizure frequency decrease of 41.3%, this decrease was not sustained throughout the open-label phase. Patients 1, 5, 9, and 12 had sustained response, with reduction in their seizure frequency during the open-label phase (18%, 45.3%, 22.6% and 12.8%, respectively). However, there has being no statistically significant decrease and none of the patients reached 50% reduction in seizure-frequency.

Table 1 Clinical characteristics of patients who completed the study and seizure frequencies in the Verapamil and placebo groups at baseline, double-blind, and open-label study phases.

Patient	Sex	Age	Underlying condition and epilepsy syndrome	Seizure types (clinical and EEG)	Brain MRI	Concurrent AEDs and doses (mg) per day		Seizure frequency (seizures/week)[a]				
							Treatment Group	Baseline	Double-blind	Seizure reduction	Open-label	Seizure reduction
1	F	22	U — frontal lobe epilepsy	FoS and FSG	Normal	LTG 900 + TPM 225 + CLZ 10	Verapamil	0.33	0.35	—	0.27	18%
2	M	33	SM — multifocal, L temporal predominance	FoS and FSG	Band like subcortical gray matter	VPA 500 + LTG 400 + VGB 3000	Verapamil	1.9	2.67	—	3.23	—
5	F	42	SM — Multifocal, R frontal predominance	FoS, FSG and GS	Normal	LTG 600 + TPM 400 + LEV + CLB	Verapamil	4.83	3.73	22.70%	2.64	45.30%
7	M	25	U — multifocal (LGS)	FoS, FSG and GS	Normal	LCS 400 + VGB 2500 + OXC 900	Verapamil	3	3.88	—	5.09	—
8	F	20	SM — R frontal	FoS and FSG	FCD (R anterior cingulate gyrus + R superior frontal gyrus)	CBZ 1300 + LEV 2000 + CLZ 20	Verapamil	23.54	13.82	41.30%	25.1	—
9	M	27	SM — R occipital	FoS and FSG	FCD (R mesial occipital)	CBZ 1400 + LEV 3000 + LTG 200	Verapamil	3.36	4.53	—	2.6	22.60%
12	F	19	SM — Multifocal	FoS and FSG	Migrational disorders — FCD + ulegyria	LTG 675	Verapamil	5.53	4.84	12.40%	4.82	12.80%
3	F	20	SM — L temporal	FoS	Heterotopic gray matter (resected) over L temporal, parietal and occipital lobes	LTG 700 + LEV 3000	Placebo	0.88	0.78	11.30%	0.67	23.80%
4	F	50	U — frontal lobe epilepsy	FoS	Normal	PRM 750 + LTG 600	Placebo	89	59.93	32.60%	56.31	36.70%

Table 1 (*Continued*)

Patient	Sex	Age	Underlying condition and epilepsy syndrome	Seizure types (clinical and EEG)	Brain MRI	Concurrent AEDs and doses (mg) per day		Seizure frequency (seizures/week)[a]				
							Treatment Group	Baseline	Double-blind	Seizure reduction	Open-label	Seizure reduction
6	F	25	U — frontal lobe epilepsy	FoS and FSG	Normal	LTG 500 + CBZ 800 + PRM 1000 + CLZ 60	Placebo	21.21	29.56	—	31	—
10	F	33	SM — multifocal	FoS and FSG	CC agenesis, colpocephaly and R hemisphere atrophy	LEV 3000	Placebo	0.52	1.48	—	1	—
11	M	63	U — L temporal	FoS and FSG	Normal	CBZ 800	Placebo	1.21	0.81	33%	0.64	47.10%

Abbreviations: CC: corpus callosum; FCD: focal cortical dysplasia; FoS: focal onset seizures; FSG: focal seizures with secondary generalization; G: genetic etiology; GS: generalized seizures; SM: structural or metabolic etiology; U: unknown etiology. AEDs abbreviations: CBZ: carbamazepine; CLZ: clobazam; LCS: lacosamide; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PRM: primidone; TPM: topiramate; VPA: valproic acid.

[a] Statistics: A non-parametric Friedman two-way ANOVA test with Bonferroni post hoc correction was used: the average seizure frequency of the patients in the verapamil group did not significantly change from baseline in either the double-blind or open-label study phases ($104.8 \pm 11.9\%$ in double-blind; $p = 0.86$, and $106.8 \pm 17.3\%$ in open-label; $p = 0.80$). There were no significant differences between the average seizure frequency between baseline, double-blind, and open-label groups in the placebo group ($129.2 \pm 40.7\%$ in double-blind; $p = 0.37$, and $106.0 \pm 27.0\%$ in open-label; $p = 0.85$). The average seizure frequency of patients in the verapamil group versus the placebo group at the double-blind study phase failed pass significance ($104.8 \pm 11.9\%$ in verapamil versus $129.2 \pm 40.7\%$ in placebo, $p = 0.41$). The average seizure frequency in the open-label study phase between verapamil and placebo groups was also not significantly different ($106.8 \pm 17.3\%$ in verapamil versus $106.0 \pm 27.0\%$ in placebo, $p = 0.98$).

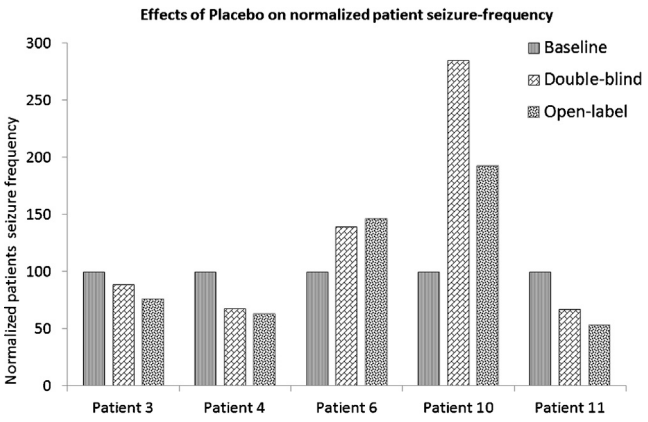

Figure 2 Effects of placebo on normalized patient seizure-frequency. This histogram shows the normalized patient seizure frequency in the placebo group. Patients 3, 4, 10 and 11 had a decrease in seizure frequency ranging from 23.8% to 47.1% when placed on verapamil during the open-label phase. However, it is uncertain whether this seizure reduction was a result of the verapamil treatment or if it represents the natural history of these patients (3, 4 and 11), since their seizure frequency was decreasing even in the double-blind phase when they were receiving only placebo.

between the average seizure frequency between baseline and double-blind ($129.2 \pm 40.7\%$; $p = 0.37$), or baseline and open-label ($106.0 \pm 27.0\%$; $p = 0.85$) in the placebo group (Fig. 2). When comparing the verapamil group with the placebo group at the double-blind study phase, the average difference in seizure range also failed to show significance ($104.8 \pm 11.9\%$ in verapamil versus $129.2 \pm 40.7\%$ in placebo, $p = 0.41$). Similarly, the average difference in seizure range of the verapamil and placebo groups during the open-label phase was also not significantly different ($106.8 \pm 17.3\%$ in verapamil versus $106.0 \pm 27.0\%$ in placebo, $p = 0.98$). Despite there being no statistically significant decrease in the seizure frequency of patients receiving verapamil, some individual patients did experience lower seizure frequencies (patients 1, 5, 9, and 12; see Table 1 and Fig. 1). One patient chose to remain on verapamil following termination of the study (patient 9). These four patients had respectively an 18%, 45.3%, 22.6% and 12.8% reduction in their seizure frequency during the open-label phase. One patient (patient 8) in the verapamil group had an initial seizure frequency decrease of 41.3%, but this decrease was not sustained throughout the study. In the placebo group, four patients had a decrease in seizure frequency ranging from 23.8% to 47.1% when placed on verapamil during the open-label phase (Fig. 2). However, it is uncertain whether this seizure reduction was a result of the verapamil treatment or if it represents the natural history of these three patients; since seizure frequency was decreasing even in the double-blind phase when they were receiving only placebo (in all except patient 10).

Safety

Impact of verapamil on the levels of anti-epileptic drugs

Throughout the study the levels of standard anti-epileptic drugs were collected from the patients receiving verapamil and placebo. Baseline drug levels were set to 100% for each drug. Patients 5 and 8 (in the verapamil group) displayed an increase in their blood levels of clobazam (CLZ) after starting verapamil, averaging $145.3 \pm 9.6\%$ ($p = 0.003$) and $122.2 \pm 8.6\%$ ($p = 0.033$) of baseline levels over the course of the study, respectively (Fig. 3A). Similarly, the levels of desmethylclobazam in patient 8, but not patient 5 ($103.8 \pm 2.5\%$; $p = 0.18$), increased to $115.6 \pm 6.3\%$ ($p = 0.037$) of baseline levels after starting verapamil (Fig. 3B). Additionally, the levels of CBZ in patients 8 and 9 were significantly higher following verapamil. Patient 8 displayed an increase in CBZ level to $108.5 \pm 3.6\%$ ($p = 0.049$) in comparison with the baseline levels; and patient 9 had CBZ levels of $129.2 \pm 9.7\%$ ($p = 0.017$) that of baseline levels, and it was necessary to decrease CBZ dosage from 1400 mg/day to 1200 mg/day during visit 7 due to CBZ side effects (Fig. 3C). Finally, the blood levels of VPA in patient 2, the only patient on VPA, were significantly higher following the exposure to verapamil ($112.2 \pm 8.62\%$ baseline levels; $p = 0.033$).

Reported side effects of verapamil

Patients in both groups reported side effects throughout the study (Table 2). Of the patients in the verapamil group, two patients complained of skin rashes, one of feet edema, one of feeling faint, and one of drowsiness. The patient with feet edema withdrew from the study. In the placebo group, two patients complained of feeling faint, one of fatigue, light-headedness and nausea, one of loss of appetite with weight loss, one of irregular menses and weight gain, and another of just weight gain. Three patients in the placebo group withdrew due to side effects.

Echocardiogram and Holter monitoring results

All patients had an echocardiogram at baseline, and in all of them the heart chambers were normal, with left ventricle showing normal systolic function and normal diastolic filling. In all participants who finished the study, the 24-h Holter monitoring during baseline and after the open-label phase revealed sinus rhythm, no cardiac arrhythmias or sporadic premature beats.

Discussion

This pilot study describes the first double blind, placebo controlled trial using verapamil as add-on therapy for patients with refractory epilepsy. In our study, (i) some patients experienced lower seizure frequencies, but none of them reached 50% reduction (ii) the average seizure frequency of patients in the verapamil group did not significantly change from baseline in either the double-blind or open-label study phases; (iii) there were no significant differences between the average seizure frequency of baseline, double-blind, or open-label groups in the placebo group; (iv) comparing the average difference in seizure range of patients in the verapamil group against those in the placebo group at the double-blind study phase also failed to be significantly different; and (v) the average difference in seizure range in the open-label study phase between verapamil and placebo groups was also not significant.

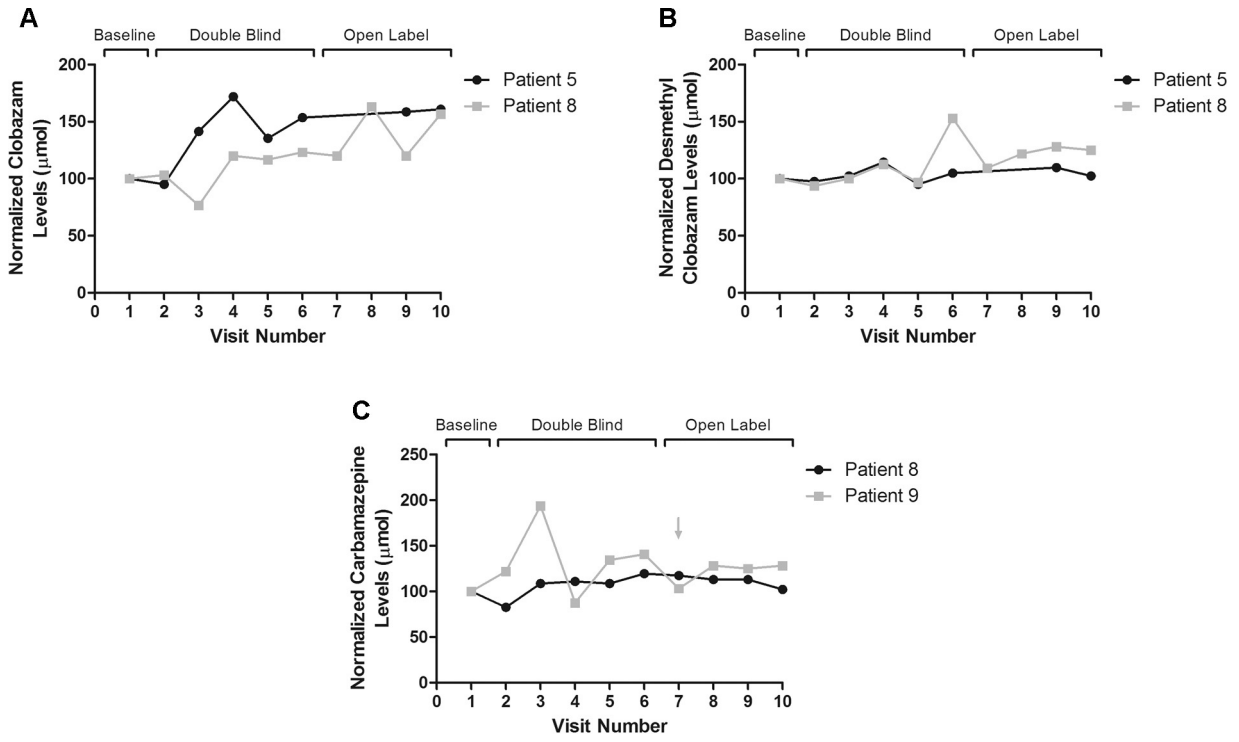

Figure 3 Anti-epileptic drug levels in patients receiving verapamil. Dot and line plots showing the levels of CLZ (A), desmethylclobazam (B), and CBZ (C) in patients receiving verapamil for each visit over the course of the study. Visit 1 represents the study baseline, visits 2—6 comprise the double-blind, and visits 7—10 comprise the open-label phase. Baseline levels were set as 100% for each individual patient with subsequent visits normalized to this value. Patients 5 and 8 displayed an increase in their blood levels of CLZ after starting verapamil, averaging $145.3 \pm 9.6\%$ ($p = 0.003$) and $122.2 \pm 8.6\%$ ($p = 0.033$) of baseline levels over the course of the study, respectively (A). Similarly, the levels of desmethylclobazam in patient 8, but not patient 5 ($103.8 \pm 2.5\%$; $p = 0.18$), increased to $115.6 \pm 6.3\%$ ($p = 0.037$) of baseline levels after starting verapamil (B). Additionally, the levels of CBZ in patients 8 and 9 were significantly higher following verapamil, requiring adjustments in CBZ due to clinical adverse effects (C). Patient 8 displayed an increase in CBZ level to $108.5 \pm 3.6\%$ ($p = 0.049$) in comparison with the baseline levels; and patient 9 had CBZ levels $129.2 \pm 9.7\%$ ($p = 0.017$) that of baseline levels.

Table 2 Reported side effects by patients in verapamil and placebo groups.

Treatment group	Side effects reported	Study status	Study withdrawal due to side effect
Verapamil	Drowsiness (1/8)	Completed	Not applicable
	Feeling Faint (1/8)	Completed	Not applicable
	Feet edema (1/8)	Withdrawal (1/1)	Yes
	Skin rash (2/8)	Completed (1/2)	Not applicable
		Withdrawal (1/2)	No
Placebo	Presyncope (2/8)	Completed	Not applicable
	Fatigue[a] (1/8)	Withdrawal (1/1)	Yes
	Irregular menses[b] (1/8)	Withdrawal (1/1)	No
	Light-headedness[a] (1/8)	Withdrawal (1/1)	Yes
	Loss of appetite and weight loss (1/8)	Withdrawal (1/1)	Yes
	Nausea[a] (1/8)	Withdrawal (1/1)	Yes
	Weight gain[b] (2/8)	Completed (1/2)	Not applicable
		Withdrawal (1/2)	Yes

The bracketed numbers in the 'side effects reported' column represent how many patients out of the total amount of patients in that drug group reported that specific side effects. The bracketed numbers in the 'study status' column represent how many patients, out of the patients who reported that specific side effect, completed or withdrew from the study.

[a] Refers to one patient who reported three different side effects and withdrew.

[b] Refers to one patient who complained about two different side effects, but completed the study.

Table 3 Clinical studies involving human patients with epilepsy who underwent adds on verapamil trial.

Study	Number of patient(s), age(s)	Patients' clinical data	Verapamil doses used	Outcome
Summers et al. (2004)	*n* = 1, 24 y	FoS and recurrent focal SE	Oral 180 mg/day, increasing up to 480 mg/day	Frequency of seizures was not measured, but interval between SE episodes widened up to 105—136 days.
Iannetti et al. (2005)	*n* = 1, 11 y	Simple partial SE followed by non convulsive SE and lately G seizures	Intravenous 0.034 mg/min (total load: 3.125 mg), followed by oral 120 mg	After SE recovery, patient had syncope and two seizures in six months. Over the following months, seizures recurred with a weekly to daily frequency.
Iannetti et al. (2009)	*n* = 2, 14 y and 4 y[a]	SMEI	Oral 1 mg/kg/day up to 1.5 mg/kg/day; (patient 1 = 35—70 mg/day; patient 2 = 17—26 mg/day)	Patient 1 — good response for 13 months. After stopped verapamil: 90% persistent myoclonic, FoS and G seizures recurred. Patient 2 — decreased myoclonias, but FoS and G persisted, no SE after a 20 month follow-up period.
Schmitt et al. (2010)	*n* = 1, 20 y	FLE, bilateral tonic seizures, and tonic refractory SE	Oral 120 mg/day	Statistically significant reduction in nocturnal seizures for 15 days, but patient was not seizure free.[b]
Pirker and Baumgartner (2011)	*n* = 1, 80 y	FoS (clonic), refractory SE	Intravenous 5 mg, followed by enteral120 mg/day	Intravenous dose immediately stopped the seizures, but patient died after 14 days due to heart and renal failure.
Wical and Wandorf (2013)	*n* = 5, 3—18 y [a]	GTCS, and FoS with secondary generalization	Oral 4—8 mg/kg/day	1 child did not improve (6 weeks); 4 children had 40—80% reduction in seizures (29, 21, 4, and 3 months old).
Asadi-Pooya et al. (2013)	*n* = 19, mean age 31.7 y (18—53)	Refractory TLE	Oral 120 mg (*n* = 13); oral 240 mg (*n* = 6)	36.84% of patients reached 50% reduction in seizures, particularly in the 240 mg group (50% = 3 patients). 17/19 had side effects, 14 mild or transient.
Nicita et al. (2014)	*n* = 7, mean age 11 y (4—18)	SMEI *n* = 4 (3*); LGS *n* = 1; symptomatic epilepsy *n* = 2	Oral 1—1.5 mg/kg/day	3 SMEI* patients partially responded[c]; 1 SMEI and 1 LGS patient had a brief period of control followed by worsening; 2 patients with symptomatic epilepsy did not have any improvement.

Abbreviations: FLE: frontal lobe epilepsy; FoS: focal onset seizures; G: generalized; GTCS: generalized tonic clonic seizures; SMEI: severe myoclonic epilepsy in infancy; SE: status epilepticus; TLE: temporal lobe epilepsy.

[a] SCN1A gene mutation.

[b] Authors: ''the natural course of SE could have coincided with the observation periods''.

[c] Favorable response in terms of seizure control and cognitive performance, although any standardized scale was applied.

The main limitation of the present study was our sample size. This is a small study, albeit only one previous open label had more patients, with a heterogeneous population. We had difficulties recruiting new patients and an important nocebo effect was observed.

In this pilot double-blind study, cardiac side effects of verapamil were not observed. Mild and transient side effects led to discontinuation of only 1 patient of the verapamil group. In fact, mild side effects were also observed in the placebo group, in which three patients withdrew. Thus, verapamil in doses up to 240 mg seemed safe and well tolerated. The reported side effects unique to the verapamil, skin rashes and feet edema, are not surprising as these side effects have been known to be associated with verapamil. However it is important to note that verapamil increased the concentration of other AEDs, and some of them had to be adjusted during the study.

Multidrug transporters like P-gp limit the access of AEDs to their site of action, lowering AED concentration at the epilepsy focus and rendering the epilepsy refractory to conventional medical treatments (Schmidt and Löscher, 2005; Löscher, 2005; Tishler et al., 1995). In fact, hippocampal neurons from rats and humans with refractory TLE have been shown to over-express the human multidrug resistance-1 gene (*MDR-1*) (Sisodiya et al., 2002; Marchi et al., 2004; Volk et al., 2004), which encodes for P-gp. Given that several AEDs or their metabolites are substrates of P-gp, we worked with the hypothesis that verapamil, which is a P-gp inhibitor, would decrease the efflux of AEDs from epileptic brain tissue back into blood vessels.

Interestingly, verapamil may also interfere with the bioavailability of AEDs due to its interactions with cytochrome P450 (CYP3A4) and conjugation enzymes (UGT1A4) (Ghosh et al., 2011, 2013). It has been shown that CYP3A4 and UGT1A4 have expression at variable levels in neuronal tissue and at BBB levels in the epileptic brain, and the enzymatic systems blockage by verapamil may increase AED levels in neuronal tissue (Ghosh et al., 2010, 2011, 2013).

Previous uncontrolled studies have shown the effects of verapamil in reducing the seizure frequency of status epilepticus and drug-resistant epilepsies. The first two reports of verapamil being used in humans were restricted to patients in status epilepticus with focal onset seizures. In both patients there was a good initial response that failed to continue over the following months with neither patient experiencing seizure freedom at any point during the verapamil treatment. The first of these patients received 180 mg/day (up to 480 mg) (Summers et al., 2004) and the second received 120 mg (after an intravenous load of 3.125 mg) (Iannetti et al., 2005). Four years later, two other patients (ages 4 and 14) with SMEI had verapamil added onto their AED regimen (Iannetti et al., 2009). Again, both patients seemed to have some initial, but not sustained, beneficial response. Finally, two other single cases have been reported. In one case, a 20 y-old woman with frontal lobe epilepsy had a statistically significant reduction in nocturnal seizures for 15 days when 120 mg of verapamil was given to her, although still not achieving a seizure free status (Schmitt et al., 2010). In the other case, an 80 y-old patient with focal clonic seizures, which had evolved to refractory status epilepticus, stopped having seizures immediately after administration of 5 mg intravenous verapamil in addition to LEV, VPA and IV midazolam. The patient was kept on 120 mg of enteral verapamil, LEV and midazolam were substituted by CBZ and CLZ; unfortunately the patient died 14 days later due to heart and renal failure (Pirker and Baumgartner, 2011).

More recently, three other open label studies have shown benefits of verapamil (Wical and Wandorf, 2013; Asadi-Pooya et al., 2013; Nicita et al., 2014). Once again, in a homogeneous group of 19 patients (mean age 31.7 y/o) with TLE, 7 of 19 cases (36.84%) reached 50% or more reduction in seizure frequency (Asadi-Pooya et al., 2013). On the other hand, another study including seven patients (ages between 4 and 18 y/o) with multiple etiologies has shown inconsistent results. Three patients with SMEI due to a *SCN1A* mutation partially responded, while one SMEI patient with no gene mutation and another Lennox—Gastaut patient had a brief period of control followed by worsening. Moreover, two patients with symptomatic epilepsy did not have any improvement. The authors hypothesized that maybe verapamil could be helpful particularly for patients with *SCN1A* mutations, as in addition to its effects on P-gp action it would also restore Ca^{2+} and K^{+} equilibrium through its effects on ionic membrane channels (Nicita et al., 2014). In fact, recent findings presented at the Child Neurology Society meeting of 2013 may support this theory (Wical and Wandorf, 2013). Out of the five patients with *SCN1A* mutations (ages between 3 and 18 y/o) who received verapamil, one child did not have any improvement after 6 weeks, whereas the other four children experienced reduced seizure frequencies (40—80% reduction of generalized tonic—clonic and secondarily generalized seizures) after follow up periods ranging from 3 to 29 months (Wical and Wandorf, 2013). Important to note though is the higher doses used in this study, ranging from 4 up to 8 mg/kg/day, as opposed to previous child studies. This, as well as the uniformity of the sample group, and lack of a placebo arm might explain why this study observed improvements while some other studies did not. The results from all previous clinical studies involving human patients with epilepsy receiving verapamil are summarized in Table 3.

In contrast to these studies, none of our patients reached a 50% or more reduction in their number of seizures. The best response we had was in a 20 y-old patient with frontal lobe epilepsy due to cortical dysplasia (patient 8, 41.3% seizure reduction) and even then, the response was not sustained through the open-label phase. Interestingly, another patient with cortical dysplasia (patient 9) did not have any seizure reduction in the double-blind phase of the study, but his seizures did decrease by 22.6% in the open-label phase and after the study concluded, the patient decided to continue taking verapamil in addition to his other three AEDs.

Conclusions

In this pilot study only a partial response was obtained in a subset of refractory patients treated with verapamil as add-on therapy for focal-onset seizures. None of patients had 50% or greater reduction in seizure frequency and no statistically significant differences were found between verapamil and placebo group responses.

Possible reasons for the lack of a significant effect could be the heterogeneity of our sample, the dose of verapamil used (although this is standard and is the dose used in most open label trials), other unknown mechanisms of drug resistance, and the small number of patients enrolled in this trial. Even in the absence of prior placebo-controlled studies, we recognize published findings showing that verapamil seems to be helpful for patients with *SCN1A* mutations or those with focal onset seizures due to TLE. Further placebo-controlled studies on those groups would help clarifying the role of verapamil as an add-on therapy in human epilepsies.

Conflict of interest

None of the authors has any conflicts of interest to disclose.

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