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

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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