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Adjunctive use of verapamil in patients with refractory temporal lobe epilepsy: A pilot study

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ABSTRACT

Objective: The present study aimed to determine if adjunctive use of verapamil, as a P-glycoprotein (P-gp) inhibitor, is efficacious in decreasing seizure frequency in patients with refractory temporal lobe epilepsy.
Materials and methods: This was an open-label pilot study. Adult patients with refractory temporal lobe epilepsy were studied. Baseline seizure type and seizure count were determined. Patients were divided randomly into two groups. Group A received verapamil 120 mg/day (n = 13), and group B received 240 mg/day (n = 6). All patients were followed for eight weeks. The proportion of responders, which consist of patients with more than 50% reduction in seizure frequency from baseline, was tabulated.
Results: Nineteen patients were studied. Seven patients (36.84%) reached the responder rate. Three patients (50%) in group B were among the responders; two of these patients achieved seizure freedom. Four patients (30.7%) in group A responded favorably to verapamil.
Conclusion: Developing new means of improving the effectiveness of existing antiepileptic drugs is a desirable way of tackling the dilemma of medically refractory epilepsy. Hypothetically, P-gp inhibitors (e.g., verapamil) might be used to counteract the removal of AEDs from the epileptogenic tissue. Such a strategy was adopted in this non-placebo-controlled, open-label, pilot study. We observed a significant achievement in seizure control associated with adjunctive use of verapamil in patients with refractory temporal lobe epilepsy.

1. Introduction

For many years, the epilepsy community has addressed the burden of drug-resistant epilepsy by concentrating on the development of new antiepileptic drugs (AEDs) and epilepsy surgery. These approaches have resulted in some improvement, but the percentage of patients with refractory epilepsy is still substantial [1–3]. To date, no study has demonstrated that the new AEDs have greater potency than more established AEDs. On the other hand, only a small percentage of patients whose seizures had failed to respond to initial monotherapy achieved seizure freedom with alternative monotherapy, and a very small percentage became seizure-free on combination therapy [4]. In addition, epilepsy surgery is an invasive procedure, sometimes with significant adverse effects [5].

Two major mechanisms have been put forward in medically refractory epilepsy: (a) removal of AEDs from the epileptogenic tissue through excessive expression of multidrug efflux transporters such as P-glycoprotein (P-gp) and (b) reduced drug-target sensitivity in epileptogenic brain tissue [6,7]. P-glycoprotein, the encoded product of the human multidrug resistance-1 (MDR-1; ABCB1) gene, is of particular clinical relevance in the emergence of multidrug resistance (MDR), which plays an important role in the treatment failure of tumors, infectious diseases, and epilepsy [7]. It has been shown that MDR-1 is overexpressed in brain tissue (hippocampal neurons) from rats and patients (humans) with medically refractory temporal lobe epilepsy [8–10]. It is proposed that P-gp is overexpressed at the luminal side of the brain capillary endothelial cells where it acts as an efflux pump to lower the interstitial concentration of AEDs in the vicinity of the epileptogenic pathology and thereby render the epilepsy resistant to treatment with AEDs [8–11]. For direct proof of this theory, it should be examined whether P-gp inhibitors can be used to counteract multidrug resistance [6,7]. Such a strategy is suggested by a report on a patient with medically refractory epilepsy in whom the P-gp inhibitor "verapamil" was added to the AED regimen. This addition greatly improved seizure control [12].

Several compounds already in clinical use, including verapamil, nifedipine, quinidine, amiodarone, nicardipine, quinine, tamoxifen, and cyclosporin A, are able to inhibit P-gp [13]. Verapamil hydrochloride is a calcium-channel blocking agent, which is usually used in the management of tachyarrhythmias, angina, hypertension, and acute myocardial infarction [14]. This drug has also been used with some success in the management of manic manifestations of bipolar disorder [15,16].

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Neurologists sometimes prescribe verapamil for prophylaxis of migraine headaches [17]. The usual initial adult dosage of oral verapamil for cardiac problems is at least 120 mg/day. Verapamil is usually well tolerated in therapeutic dosages [14].

This study was conducted to determine if adjunctive use of verapamil, as a P-glycoprotein inhibitor, in patients with refractory temporal lobe epilepsy (RTLE) is efficacious in decreasing their seizure frequency. We also tried to investigate the safety and tolerability of adjunctive use of verapamil in patients with RTLE.

2. Materials and methods

This was an non-placebo-controlled, open-label, pilot study with convenience sampling from one center (outpatient epilepsy clinic at Shiraz University of Medical Sciences). Inclusion criteria were as follows: male/female (nonpregnant female adequately protected from conception) patients, between the ages of 18 and 65 years; with diagnosis of temporal lobe epilepsy made on the basis of clinical findings; and with medically refractory seizures defined as failure of two or more AEDs at maximal tolerated dosages and one or more seizures per month. They had stable medication regimens for four weeks prior to entry. Informed consent by patients was obtained. Exclusion criteria were as follows: patients with progressive neurological conditions; patients with cortical malformation, dysplasia, schizencephaly, lissencephaly, and other malformations of development; patients with a history of noncompliance for seizure diary completion or frequent clinic visits; patients taking levetiracetam as monotherapy (levetiracetam does not seem to be transported by P-gp at the blood–brain barrier [18]); patients having any serious medical illness or major psychiatric disorder, history of nonepileptic seizures, or history of suicidal attempt in the past five years; patients with any known contraindication for verapamil administration including severe GI narrowing, heart failure, hypertrophic cardiomyopathy, cardiac conduction disturbances, hypotension, hepatic impairment, renal impairment, and known history of hypersensitivity to verapamil; and patients taking any other medication with significant drug interaction with verapamil.

In the first visit, signing of informed consent, enrollment and registration, baseline blood pressure (BP) determination, and an electrocardiography (ECG) study were done. In the second visit (8-week baseline), seizure types (complex partial and generalized tonic–clonic seizures) and seizure count were determined. Starting from this visit, all eligible patients received oral verapamil as 40-mg tablets three times a day on a daily basis. These patients were divided randomly into two groups. Group A was titrated to a dosage of 40 mg three times a day in one week ($n = 11$), and group B was titrated to a dosage of 80 mg three times a day in two weeks ($n = 9$), after confirming the tolerability of the patients to the previous dosage and checking their vital signs and ECG in an office visit. All patients were followed for eight weeks after their titration period. The previously prescribed AEDs were continued during the study with dosages similar to the baseline evaluation period. Follow-up visits were scheduled at the 12th and 17th (in group A) and 18th (in group B) weeks to determine the seizure types and seizure count and also to determine the safety and tolerability of adjunctive use of verapamil in these patients. All patients received free verapamil and were offered free visits and free ECGs during the study period.

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. The proportion of responders, that is, patients with more than 50% reduction in seizure (complex partial seizures and generalized tonic–clonic seizures) frequency from baseline and mean percentage reduction in seizure frequency, was tabulated. Based upon published trials of new antiepileptic drugs, we would hope that at least 25% of patients would have a response (>50% reduction in seizure frequency) to consider this pilot study successful [19–23]. This study was conducted in accordance with local ethical regulations with approval by Shiraz University of Medical Sciences Review Board and Ethics Committee (IRCT # 2012121711778N1 and grant # 90-01-01-3629). All patients consented in writing to their participation after the scope of the study had been explained in a form understandable to them. The collected data were kept confidential through codes. All patients were advised that verapamil was not an approved therapy for epilepsy. The patients were informed of untoward drug effects related to their AEDs or verapamil and were instructed to report them or any other adverse effects immediately to the physician.

3. Results

3.1. Patients

Twenty patients with confirmed refractory temporal lobe epilepsy were included in the study (six men and 14 women). The mean age of the patients was 31.7 ± 9.1 years. The mean age at seizure onset was 17.6 ± 11.4 years; the mean seizure duration was 15.16 ± 8.27 years. In three patients from group B, the dosage of verapamil was reduced from 240 mg/day to 120 mg/day because of intolerable adverse events; they were entered into group A. One patient from group A had poor drug adherence, and she was excluded from the study. Therefore, there were 13 patients in group A (120 mg/day) and six patients in group B (240 mg/day). All patients were adherent to their drug regimens (both antiepileptic drugs and verapamil). The characteristics of the patients and their clinical variables are summarized in Tables 1 and 2.

3.2. Efficacy

Seizure count and the responder rate (the proportion of patients experiencing a 50% or greater reduction in their seizure frequency, compared with their baseline) were evaluated. Seven patients (36.84%) reached the responder rate. Three patients (50%) in group B were among the responders; two of these patients achieved seizure freedom (they were seizure-free during the entire treatment period), and one patient experienced more than 95% seizure reduction. This latter patient discontinued his carbamazepine for one day (because he thought he was relieved by verapamil) and experienced one GTCS. He did not experience any more seizures after restarting his carbamazepine. Four patients (30.7%) in group A responded favorably to verapamil. The mean

Table 1
Characteristics of the patients studied.

Patient	Age (years)	Gender	Age at seizure onset (years)	Seizure duration (years)	Etiology
1	40	Male	20	20	MTS
2	18	Female	5	13	MTS
3	21	Female	17	4	Unidentified
4	42	Female	37	5	Unidentified
5	45	Female	42	3	MTS
6	34	Female	23	11	MTS
7	28	Male	12	16	Unidentified
8	26	Female	11	15	MTS and left parietal encephalomalacia (dual pathology)
9	23	Female	13	10	MTS
10	29	Male	24	5	MTS
11	28	Female	9	19	MTS
12	53	Male	24	29	MTS
13	44	Female	40	4	Unidentified
14	30	Male	6	24	Unidentified
15	32	Female	3	29	MTS
16	25	Female	16	9	MTS
17	29	Female	7	22	MTS
18	34	Female	8	26	MTS
19	34	Male	20	14	MTS

MTS: mesial temporal sclerosis.