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Short communication

Low dose verapamil as an adjunct therapy for medically refractory epilepsy – An open label pilot study

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ABSTRACT

Previous studies using verapamil as an adjunct therapy to anti-seizure medications have used doses ranging from 120 to 240 mg per day. However, despite showing promising results, there was an increased incidence of side effects. The aim of this study is to assess the efficacy and tolerability of low dose verapamil (20 mg p.o. tid) as adjunct therapy to patient's anti-seizure medications irrespective of the type or etiology of the epilepsy. In an open-label pilot study we enrolled 20 adult patients with history of epilepsy who continued to have a minimum of 2 seizures a month despite being on or having tried maximum tolerated doses of 3 or more standard antiepileptic drugs under the supervision of an epileptologist. 10 of the 19 patients (53%) who continued in the study had >50% reduction in seizure frequency. 2 of the patients (10%) had <50% seizure reduction. The remaining 7 patients (37%) had no reduction in their seizures. There was no discontinuation due to adverse events. P-Glycoprotein is a prototypical drug transporter that has been strongly implicated in drug resistance in epilepsy. Verapamil at a relatively low dose was well tolerated compared to previous studies which used up to 240 mg per day and seems to have contributed to a statistically significant improvement in seizure control in patients with medically refractory epilepsy, especially in patients with Lennox-Gastaut syndrome. A randomized double blind controlled study at this low dose with larger sample size may be more informative.

1. Introduction

Epilepsy is a major public health problem that affects 0.6–1% of the general population (World Health Organization, 2016). Most efforts are targeted to the development of increasing numbers of anti-epileptic drugs (AEDs) – more than 20 AEDs are used clinically today. However, despite the availability, 30–40% of patients do not respond to pharmacotherapy and continue to have "uncontrolled" or "refractory" seizures – a condition termed drug-resistant epilepsy (Kwan et al., 2010).

There may be multiple mechanisms to explain all forms of pharmacoresistance to the majority of the AEDs. Proposed mechanisms for pharmacoresistance involve either a) alteration in specific drug targets and/or b) less uptake of the drug into the brain. The latter is probably due to non-specific mechanisms like decreased drug uptake into the brain, perhaps due to the activity of drug efflux transporters such as P-glycoprotein (P-gp), in the blood brain barrier (BBB) (Kwan and Brodie, 2005; Löscher and Potschka, 2002; Löscher and Potschka, 2005). A large variety of lipophilic drugs including AEDs are substrates of P-gp and if we can inhibit the binding of specific AEDs to P-gp, we may be able to make an impact on treatment of drug resistant epilepsy (Kwan and Brodie, 2005; Löscher and Potschka, 2002; Löscher and Potschka, 2005).

Verapamil and nifedipine – two of the FDA approved calcium channel blockers are known to be P-gp inhibitors and in their presence, the AED levels in the brain are seen to be higher (Kwan and Brodie, 2005; Löscher and Potschka, 2002; Löscher and Potschka, 2005). Some studies have shown that verapamil can be beneficial in improving seizure control in certain groups of patients with drug resistant epilepsy and there are reports of efficacy of verapamil in isolated cases of refractory status epilepticus as well (Asadi-Pooya et al., 2013; Borlot et al., 2014; Nicita et al., 2014; Nicita et al., 2016). However, these studies were done in specific groups of patients and used up to 240 mg a day of verapamil resulting in a significant percentage of patients dropping out because of inability to tolerate the addition of verapamil. This could be related to the patients either not tolerating verapamil itself, or in combination with the AEDs,

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Table 1
Patient demographics.

ID	Age	M/F	Epilepsy type	Anti-epileptic medications used with verapamil	Adverse effects	>50% Seizure reduction	<50% Seizure reduction
1	32	F	Partial	Phenobarbital, Carmabamazepine, Lamotrigine	None	No	
2	52	M	Partial	Phenobarbital, Lacosamide, Levetiracetam	Gastrointestinal discomfort	Yes	
4	32	M	Partial	Oxcarbazepine, Clobazam, Clorazepate	None	No	
5	64	M	Partial	Oxcarbazepine, Lamotrigine, Clonazepam	Mild lightheadedness	Yes	
6	38	F	Partial	Phenytoin, Zonisamide, Clobazam, Levetiracetam	None	Yes	
7	52	M	Partial	Carbamazepine, Levetiracetam	None	No	Yes
8	23	F	Lennox-Gastaut Syndrome	Phenytoin, Valproic acid, Levetiracetam, Clobazam	None	Yes	
9	21	F	Lennox-Gastaut Syndrome	Valproic acid, Zonisamide, Levetiracetam	None	No	
10	55	M	Partial	Lamotrigine, Primidone, Levetiracetam	None	No	
11	71	F	Partial	Lamotrigine, Primidone	Fatigue	No	
12	32	F	Partial	Lamotrigine	None	No	
13	20	M	Lennox Gastaut Syndrome	Lamotrigine, Levetiracetam, Clobazam	None	Yes	
14	49	F	Partial	Carbamazepine, Levetiracetam, Lacosamide	None	Yes	
15	18	M	Lennox Gastaut Syndrome	Clobazam, Ethosuximide, Valproic acid, Gabapentin	Agitation	No	Yes
16	63	F	Partial	Zonisamide, Lamotrigine, Levetiracetam	None	Yes	
17	21	F	Partial	Lamotrigine, Levetiracetam	None	Yes	
18	47	M	Partial	Oxcarbamazepine, Levetiracetam	None	No	
19	29	F	Partial	Phenytoin, Lacosamide, Clonazepam	None	Yes	
20	21	M	Epilepsy with both generalized and focal features	Valproic acid, Clobazam	Agitation	Yes	