The Effect of Oral Verapamil on the Visual Evoked Potentials in Multiple Sclerosis Patients

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Abstract-

Background & Aims: Ionic channel rearrangements through demyelinated axons or supporting media play a significant role in remission of neurological deficits in multiple sclerosis (MS) patients. The role of calcium channel blockers on the MS demyelination sequels is controversial. We studied the change of visual evoked potential (VEP) P100 induced by verapamil in MS patients.

Materials & Methods: We conducted a randomized double blind, placebo controlled, clinical trial on two groups of 20 clinically definite MS patients who had no relapse during the previous one year. Changes in P100 latency were compared between subjects taking 3 dosages of oral verapamil 40 mg, every 8 hours and subjects taking placebo.

Results: In the verapamil group, the P100 latencies shortened an average of 6.1±4 ms compare to placebo group 1±0.5 ms ($P<0.05$). Verapamil had no significant effect on the VEP duration.

Conclusion: The present study suggests pharmacological manipulation of calcium-dependent process, possibly at the level of demyelinated axon, can rapidly facilitate conduction of electrical impulses in visual pathways of stable MS patients.

Key Words: Maltiple Sclerosis, VEP, Verapamil, Electrophysiology, Calcium blocker

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disease that usually begins in young adults. Pathologically, it is characterized by multiple areas of CNS white matter inflammation, demyelination and glial scarring (sclerosis). The cause remains elusive, but autoimmune mechanisms, possibly triggered by environmental factors in genetically susceptible individuals, are probably important[1,2].

Remyelination in MS plaques, particularly following the acute phase, is thought to result from the differentiation of a precursor cell, type II astrocytes and oligodendrocytes. Clinicopathologic observations indicate that, while a small degree of remyelination may occur at the margins of the plaques that are characteristic of MS, remissions can occur in the context of persis-

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tent demyelination, i.e., without significant remyelination within the core of the plaques[2]. Restoration of impulse conduction along demyelinated axons involves a remodeling of the axon membrane, which acquires a higher than normal density of sodium channels[3].

As remyelination proceeds, new nodes of Ranvier are formed in regions that previously are internodal. The results suggest that Na+ channels at new nodes of Ranvier come neither from original nodes nor from oligodendrocytes. They may represent a moderate aggregation of existing internodal channels. New nodes seem to possess a gradient of Na+ channel density that is much less steep than that at original nodes[4].

The calcium influx via voltage-gated calcium channels (VGCC) also plays a significant role in the development of neurological disability and white matter damage in experimental allergic encephalitis (EAE) and MS. Calcium influx also appears to play a critical role in the cascade of events leading to secondary injury after spinal cord trauma[3].

It is well established that vapamil inhibits transmission flux of calcium in virtually all tissues studied to date. Verapamil is known to enter the central nervous system in small but measurable quantities. Recently, binding sites for calcium antagonist in human brain have been identified[3]. Although only small concentrations are found within normal brain, it is possible that the defective blood brain barrier in areas of presumed demyelination may allow higher central nervous system (CNS) verapamil concentrations in patients with multiple sclerosis than in controls[5]. The mechanism whereby verapamil alters electrical transmission in CNS is unknown but may reflect antagonism of calcium-dependent processes within demyelinated axon membrane itself[5].

Conceivably, verapamil could modify the ionic flux of calcium through demyelinated axon membrane, and alter local electrical fields. This would have an effect on the sodium channel voltage sensors to alter the rate of sodium inactivation similar to sub-threshold depolarization. Alternatively, verapamil could modify calcium dependent, voltage sensitive potassium channels. There is evidence to suggest that potassium conductance is increased in areas of demyelination compared to normal axons. A drug such as verapamil may produce an indirect effect on potassium channels. It would be expected to have smaller effects on the evoked potential (EP) in normal and MS patients without demyelinated evoked pathways since potassium conductance make comparatively less contribution during normal salutatory conduction[5].

Visual, auditory, and somatosensory stimuli are small electric signals produced by neural structures along the corresponding sensory pathways. Changes in EPs produced by disease states generally consist of delayed responses, reflecting conduction delays in responsible pathways, or attenuation or loss of component waveforms, resulting from conduction block or dysfunction of the responsible generators. EPs have been utilized in order to monitor neurophysiological status of MS patients[6]. Visual evoked potential (VEP) is noninvasive and has excellent temporal resolution, thus permitting the study of dynamic changes occurring in the nervous system.

Verapamil-induced changes in the central conduction in patients with MS have been studied by Gilmore RL. and his colleagues in 1985[5]. That study investigated the effect of intravenous verapamil on brain stem auditory, visual, and somatosensory evoked potentials in MS patients. All these evoked potentials were altered toward normalization by intravenous verapamil. They suggested pharmacological manipulation of calcium-dependent process, possibly at the level of demyelinated axon, could acutely facilitate central conduction of electrical impulses in some patients with clinically stable MS. The results of these studies expanded the observations of Schauf and Davis on the transient beneficial clinical effects of systemic hypocalcaemia in MS patients[5]. Verapamil hydrochloride was used in the treatment of 11 patients with MS by Komoly S and his colleague in 1986[6]. The rationale of the therapy was to improve the conduction capacity of the damaged nerve fibers. The therapy did not prove the effectiveness in this pilot trial. Recently protective role for the calcium channel blockers was shown by Brand-Schieber E in one study in 2004[3]. They suggested that administration of the calcium channel blockers (CCB) bepridil and nitrendipine

significantly ameliorated EAE in mice, compared with vehicle-treated controls.

The infusion route of verapamil has a more potential side effect, but peak plasma concentrations of immediate release formulations of oral verapamil are reached between 1 and 2 hours after oral administration[7].

In this study, we observed the effect of oral verapamil on VEPs in MS patients. Our reasons to use visual evoked potentials (VEPs) in this study were:

1. VEPs are stable over a long period of time in a given patient without a clinical exacerbation. The those VEP changes associated with verapamil administration are likely to be causally related and not the result of spontaneous electrophysiological improvement[5,8].
2. VEPs afford an objective, non-invasive, and reproducible measurement of pharmacological intervention[5].
3. VEPs appear to be sensitive to small changes in various metabolic and physical parameters[9].

MATERIALS AND METHODS

We conducted a randomized clinical trial on two groups of 20 clinically definite multiple sclerosis patients (aged 17-40). Each patient had a clinical MS course for a minimum of three years. They were selected according to the following inclusion criteria:

1. Absence of a clinical exacerbation during the preceding year in order to minimize the possibility of spontaneous electrophysiological changes during the 24 hour of study,
2. No cardiac disorder or contraindication for verapamil administration or using any calcium channel blocking agents.

All patients gave their informed consent. No individual was taking medication known to affect body temperature or multiple sclerosis such as corticosteroid.

We used verapamil 40 mg every 8 hours for one day and a placebo with the same dosing interval.

As verapamil is not routinely used in patients with MS, there are no ethical point to use of placebo in theses patients.

The patients, VEP technologist and our statistical analyzer were blinded to the code. Each patient consumed his drug after performing VEP and at least 8 hour after his last dose, second VEP was done. Visual evoked potentials were obtained using a patterned-reversal check board generated by a Medtronic stimulus recorder (Medtronic, Denmark) and the analysis was done by Keypoint software. The pupils were not dilated. A series of 12×12 checks were used for pattern shifting. The pattern reversal rate was 2 Hz. Scalp electrode was placed at Oz and reference electrode was at Fz and ground was on the hand. The signal effecting the reversal of the check board triggered a computer average, The signals were amplified and filtered with band pass frequencies of 1 Hz to 1000 Hz. Two hundred responses were averaged and replicated. In evaluating VEPs, the latency of the major positive component (P100) was measured.

We used Microsoft office Excel spread sheets as our data entry software. Then data were transferred to SPSS for analysis. T-test was used to compare P-100 between the study groups. Each eye was analyzed separately to increase our sample size.

RESULTS

The patients had a mean age of 28.7 ± 7 years with no significant difference between the two groups. There were 18 women and 2 men in each group.

Last attack occurred 17.4 ± 3 months before study.

Table 1 shows the distribution of VEP abnormalities in the study groups. No patient had absent VEP in the

Table 1. *Differences between the verapamil and placebo groups before treatment*

	Verapamil	Placebo
Age (year)	29.1	28.5
Last attack (months)	17.9	17.0
VEP:		
Normal	4	4
Abnormal-unilateral	3	4
Abnormal-Bilateral	2	2

There were no significant differences between two groups in these variables.

beginning.

The pre-treatment P100 latency was abnormal in 60% of our patients (normal < 108 ms) with mean of 113 ±22 ms at the base line. The mean P100 latencies had no significant difference between groups before verapamil administration (Table 2).

During the study, no patient showed significant drug side effects. One of our patients in the verapamil group had 205 ms in P100 latency which showed 81 ms difference after verapamil administration. The original data might be a technical error. Exclusion of this patient, no significant effect was noted on the statistical analysis.

In the verapamil group, the P100 latencies shortened an average of 6.1±4 ms compared to placebo group with the latency difference of 1±0.5 ms (Table 2). This difference was significant in the studied group ($p<0.05$).

There were no significant differences on N75 and N135 latencies and VEP wave durations between two groups.

Table 2. P100 latency at baseline and its changes after treatment in the verapamil and placebo group

P100 latency (msec)	Verapamil (No=20)	Placebo (No=20)
Before Treatment (msec)	115.2 (5.5)*	111.1 (4.4)*
Change after treatment** (msec)	6.1 (4.1)*	1 (0.5)*

*numbers are standard error of means.

**the difference is statistically significant.

DISCUSSION

Rearrangements in ionic channels expression play a major role in restoration of conduction within demyelinated plaques and underlie clinical remission in patients with MS. These changes not only happen in demyelinated axons and Ranvier's nodes, but also in Purkinje and glial cells. Thus, axons and oligodendrocytes communicate in an intimate, ionically-mediated fashion, and oligodendrocytes may play an important functional role beyond that of providing the myelin sheath[10].

The mechanism whereby verapamil alters electrical transmission in CNS is not fully described but as mentioned before, may reflect antagonism of calcium-dependent processes at the level of the demyelinated axons by altering calcium-dependent cellular processes required for neural transmission.

We followed the previous study conducted by R.L Gilmore et al who used verapamil infusion and measured VEP, Brain stem auditory and somatosensory EPs. They studied only 8 patients. All EPs have been shortened in MS patients by intravenous verapamil[5]. However, another pilot study by S. Komoly these effects had not been reproduced[7].

The P100 latency change was less significant in our study than that in Gilmore's study (6.1±4 vs. 10.1±1 ms). Although we were not able to show the effect of verapamil administration on normal VEP, this should be tested on larger sample size studies.

It should be mentioned again that the magnitude of evoked potentials does not necessarily correlate with improved clinical status. Amplitude is not used for VEP evaluation in demyelinating diseases, because the most frequent abnormality is characterized by a normal amplitude but prolonged latencies of N75 and P100[1,8]. This result is not contradictory to our conclusion that verapamil has such effect on P100 latency.

The present study suggests pharmacological manipulation of calcium-dependent process, possibly at the level of demyelinated axons, can rapidly facilitate central conduction of electrical impulses in some patients with clinically stable MS.

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