Calcium Channel Blocker Verapamil: A New Intervention For High Cholesterol Levels in Patients with PTSD

Kalsiyum Kanal Blokeri Verapamil: Posttravmatik Stres Bozukluğu Olan Hastalardaki Yüksek Kolesterol Düzeyleri İçin Yeni Bir Tedavi Seçeneği

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Abstract

Objective: Most of the patients with posttraumatic stress disorders (PTSD) have higher cholesterol levels than normal subjects. Increased noradrenergic activity may trigger the induction of lipoprotein lipase, which might be responsible for the elevation in cholesterol levels in patients with posttraumatic stress disorder. Calcium ion plays an important role in stress due to its effects on brain synaptosomes. So this study was conducted to investigate the efficacy of Verapamil in high cholesterol levels in patients with PTSD.

Materials and Methods: Fifty (50) PTSD patients were selected randomly and initially enrolled in the study, from department of Psychological Medicine Dow University of Health Sciences, Karachi. Verapamil 120mg/day was given in divided doses under single blind protocol. All patients were observed and monitored weekly, throughout the duration of study. While Fifteen (15) normal control subjects apparently healthy and not taking any medication was included in study after excluding any medical illness.

Results: Verapamil showed a gradual but highly significant improvement in serum cholesterol levels in patients with PTSD.

Conclusion: Verapamil was observed to be highly effective treatment. It reduces serum cholesterol levels, and cardiovascular risk factors in patients with PTSD. *Turk Jem 2007; 11: 93-7*

Key words: PTSD, calcium channel blocker, verapamil and total cholesterol

Özet

Amaç: Posttavmatik stres bozukluğu olan hastaların çoğunda normal bireylere göre daha yüksek kolesterol düzeyleri bulunmaktadır. Artmış noradrenerjik aktivite lipoprotein lipaz aktivitesini tetiklemekte ki bu durum postravmatik stres bozukluğu olan hastalarda yüksek kolesterol düzeylerinin oluşmasına yol açıyor olabilir. Kalsiyum iyonu stress durumunda beyin sinaptozomlarında önemli bir rol oynamaktadır. Bu çalışmada verapamilin posttavmatik stres bozukluğu olan yüksek kolesterol düzeyleri olan hastalardaki etkisini araştırmak amacıyla yapıldı.

Gereç ve Yöntem: Karaçi'de Dow Üniversitesi Sağlık Bilimleri Psikiyatri kliniğinde izlenen 50 posttavmatik stres bozukluğu olan hasta rastgele yöntemle çalışmaya alındı. Verapamil 120mg/gün dozunda tek kör yöntemiyle bölünmüş dozda verildi. Tüm hastalar araştırma süresinde haftalık olarak monitorize edildi. Herhangi bir hastalığı olmayan ilaç alımı öyküsü bulunmayan sağlıklı görünümlü 15 normal birey control olarak alındı.

Bulgular: Verapamil posttavmatik stres bozukluğu olan hastaların serum kolesterol düzeylerinde yavaş fakat oldukça anlamlı iyileşmeye yol açtı.

Sonuç: Verapamilin oldukça etkili bir tedavi olduğu gözlendi. Posttravmatik stres bozukluğu olan hastalarda serum kolesterol düzeylerini düşürmekte ve kardiyovasküler risk faktörlerini azaltmaktadır. *Turk Jem 2007; 11: 93-7*

Anahtar kelimeler: Postravmatik stress bozukluğu, kalsiyum kanal blokeri, verapamil

Introduction

Posttraumatic stress disorder is one of the least researched topics in Pakistan. Terrorist attacks have been occurring frequently over the last three decades. Psychiatric complications of these disasters have not been studied systematically in Pakistan. Present study is an attempt to stress the importance of psychological and medical aspects of these incidences and their management in survivors.

There have been several studies demonstrating increased noradrenergic activity in posttraumatic stress disorders (1, 2). Psychological stress has been associated with increased noradrenergic activity in patients with PTSD. Among the patients in whom the symptoms of PTSD develop, Hawk et al. demonstrated

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the greater degree of activation of sympathetic nervous system. Similarly Steven et al. reported that enhanced noradrenergic activity during memory consolidation is associated with enhanced long-term memory in humans and elevated noradrenergic activity during memory consolidation would enhance memory storage. That catecholamine-mediated enhancement of memory consolidation for arousing and traumatic events may play a role in the re-experiencing symptoms of posttraumatic stress disorder. (5)

Most of the patients with posttraumatic stress disorders have higher cholesterol levels than normal subjects. Anticipatory anxiety and stress may be responsible for the elevations in cholesterol levels of patients with PTSD (1). Naturally and experimentally induced stress results in a significant increase in cholesterol (6).It may be that higher cholesterol levels are a result of induction of lipoprotein lipase by nor epinephrine (7).

The activity of lipoprotein lipase determines the catabolism of very low density lipoproteins (VLDL).The plasma cholesterol or low density lipoprotein (LDL) level is inversely associated with the number of LDL receptors. On the other hand catecholamines suppress the LDL receptor activity, thus leading to an increase in plasma cholesterol concentration. Regulation of the hepatic LDL receptor pathway is the dominant mechanism for controlling plasma LDL levels in human beings and the subjects with Posttraumatic Stress Disorder, who completely lack functional LDL receptors or its sensitivity, do not respond to any of the conventional dietary or drug therapies currently used to lower plasma cholesterol. The ability to modulate hepatic LDL receptor number by therapeutic agents like calcium antagonist verapamil which increases LDL receptor activity and sensitivity either per se or by decreasing the release of neurotransmitter (8-13) may forms the basis of most current therapeutic agent to lower cholesterol levels.

Hence the study was conducted and the main aim of this study was to analyze the relationship between PTSD symptoms and serum cholesterol levels, and to investigate the efficacy of Verapamil, as the treatment of high cholesterol levels in patients with Posttraumatic stress disorders.

Materials and Methods

This study was conducted in the department of Pharmacology, Karachi University, Karachi. Fifteen (15) normal control subjects apparently healthy and not taking any medication were included in study after excluding any medical illness.

Study population

This study was approved by the Research ethics committee Dow University of Health Sciences. Fifty PTSD patients were initially enrolled in the study, from department of Psychological Medicine Dow University of Health Sciences, Karachi. All the patients were expressed interest and gave the written consent to participate the study. The group of patients received diagnosis according to DSM-IV-RT (14). All patients were excluded who were taking drugs known to effect cortisol, catecholamines, urinary VMA and serum Cholesterol levels, who had a previous history of major psychiatric illness, current dependence on alcohol or other drugs of abuse like sedative or hypnotic, cardiac and liver diseases.

After explaining the limitations, consent was obtained from all study participants before enrollment. The study period consisted of nine (9) weeks for each patient, with weekly follow up visit.

Study Design

The required information such as name, age, sex, occupation, duration of disease, previous medication, laboratory investigations, dates of follow up visits, medical history and physical examination were recorded as per protocol.

The fasting blood samples were collected for assessment of serum cholesterol on week-0, thereafter patients received 40 mg of verapamil orally three times a day up to week-9 of study. At each weekly visit, all patients were fully inquired about drug compliance, side effects and intensity of symptoms related to PTSD. Patients were also motivated to keep their nutritional habits, physical activity and general life style as constant as possible throughout the study period. After completion of every 3 weeks therapy, blood samples were collected for the assessment of serum cholesterol levels.

Analytical Methods

Subject Reported Measures:

The selected patients were enrolled, data and progress of patients was recorded. From the start of study i.e. week-0 up to the end of study i.e. week-9, an observer completed the Stress symptoms questionnaire, which was based on The Clinician-Administered PTSD Scale (CAPS). It is a structured clinical interview designed to assess adults for the seventeen symptoms of Posttraumatic Stress Disorder (PTSD) outlined in DSM-IV-TR (15,16), and is commonly used as a "gold standard" diagnostic instrument for assessing PTSD (15). Subjects indicated the degree to which they had experienced each symptom during the past week on a five point scale in which 0= not at all, 1= a little, 2= moderately, 3= quite a bit and 4= extremely. The ratings for individual items were summed for a total score for each scale (Table 1).

Serum Analysis Measures:

Cholesterol Flex reagent cartridge Cat No. DF-27 was required to analyze the serum cholesterol. This test was performed on the Dimension clinical chemistry system. It is an in vitro diagnostic test intend for the quantitative determination of total cholesterol in serum and plasma.

Urine Analysis Measures:

Twenty-four hours urinary Vanillylmandelic Acid (VMA) was determined by using kit, biosystem Spain. An anionic exchange resin being eluated there after once the interfering substances are washed away retains Vanillylmandelic Acid. The VMA is quantified spectrophotometrically as Vanilin after peroidate oxidation under alkaline conditions.

The amount of VMA per 24 hours urine was calculated using the following general formula:

mg / L VMA X V Urine / 24 Hours (L) = mg VMA / 24 hours

Statistical Analysis

All data are expressed as means + standard error of the mean (SEM). Differences between means were tested for significance using the paired Student's t-test. Data analysis was performed using the Statistical Package for Social Sciences (SPSS). For all analyses, P values less than 0.05 was considered significant.

Results

Clinical characteristics and compliance of the patients

During the study it was observed that all subjects of either sex ranging in age from 25-45 years (x = 35.1 + 1.6). They all expressed interest and gave written consent to join the study.

They had a mean of 1.5 months past history of traumatic event (Range 1-3 months). All had subjective symptoms of Post Traumatic Stress Disorder, their urine specimens showed positive results when tested for 24 hours urinary VMA and their serum analysis showed elevated total cholesterol when tested for lipid profile. Treatment compliance was good in both groups and most of the patients did not report any drug related adverse effect. No abnormality was observed in complete blood counts or in renal and liver function tests after treatment with Verapamil.

Symptom severity scores

A mean score of 60.5 + 1.73 was obtained on week-0 of study. But after administration of Verapamil the PTSD symptoms score decreased to 47.9+ 1.42 on week-1, thereafter the relief of subjective symptoms was also dramatic, and symptoms were practically disappeared in the patients on week-8 and week-9 of study. (Fig 1)

24 hours urinary VMA

The patients had higher mean values of 5.84+ 0.26, 24-hours urinary VMA when compared with the values of 15 normal subjects (Control group), i.e. 2.99 + 0.68. The 24-hours urinary VMA was decreased from the mean value of 5.84+ 0.26 on week-0 to 2.70 + 0.18 on last week that is week-9 of study. Thus the effects of verapamil to decrease the release of nor epinephrine and excretion of 24-hours urinary VMA were highly significant ($P < 0.001$) on week-9 as compared with VMA values in patients on week-0 of study and non-significant when compared with normal subjects (Fig 2).

Serum cholesterol

Mean values of serum cholesterol of 235.13 + 5.12 mg/dl were obtained on pre treatment week-0, where as in control group the mean values of serum cholesterol were 181.14 + 4.45 mg/dl. Thus the difference between mean values of serum cholesterol of Verapamil and control groups at week-0 of study was statistically highly significant. However, administration of Verapamil produced a slight and negligible decrease in cholesterol levels from 235.13 + 5.12 mg/dl to 219.28 + 4.77 mg/dl on week-3. While the cholesterol levels of 183.20 + 4.93 mg/dl were obtained on week-6, and 179.52 + 4.48 mg/dl on week-9 of study which showed a non-significant difference when compared with control group. (Figure 3)

Discussion

This is the first study to our knowledge, to investigate the effects of calcium channel blocker verapamil on symptom severity scores and cholesterol levels in patients with PTSD. 24-hour urinary VMA levels were assessed as an index of activity in the sympathetic branch of the autonomic nervous system, the portion of nervous system that would underlie the presumed hyperarousal in the PTSD. In the present study, excretion of VMA was directly related with PTSD diagnosis and symptom severity among the patients as assessed with Clinician Administered PTSD Scale (CAPS). These findings are consistent with biopsycho-

Table 1. Clinician-Administered PTSD Scale (CAPS)

No.	SYMPTOMS	Study Weeks									
		0	1	2	3	4	5	6	7	8	9
1	Upset Feelings										
2	Fear or Horror										
3	Helplessness										
4	Repeated disturbing memories										
5	Palpitations										
6	Sweating										
7	Difficulty in Breathing										
8	Dreams about what happened										
9	Concentrating Difficulties										
10	Trouble falling sleep										
11	Trouble staying sleep										
12	Feeling irritable										
13	Having angry outbursts										
14	Avoiding talking about what happened										
15	Avoiding hearing about what happened										
16	Startle reactions in response to sound										
17	Startle reaction in response to movements										

5- POINT SCALE OF SYMPTOMS
0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

logical study by Yehuda, which demonstrated the sympathetic hyperarousal in PTSD. These findings support the hypothesis that enhanced noradrenergic activity during memory consolidation is associated with enhanced long-termed memory in humans.

In interpretation of our results, it is important to note the findings that focused on high concentrations of serum cholesterol and an increase of sympathetic nervous system activity, which manifested itself through an intensified 24-hours urinary VMA concentration. Increased catecholamine levels can activate lipoprotein lipase, which subsequently increases the concentrations of free fatty acids in the serum, and in the liver these fatty acids are transformed in to cholesterol, so the values of serum cholesterol in patients with PTSD were logically raised. (18)

In PTSD, however, Karlovic et al. has investigated the issue, who observed increased serum lipid concentrations in soldiers. Further, this is in complete agreement with our results; however this study included an analysis of the low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), and correlation between clusters of PTSD symptoms and serum lipid concentrations, unfortunately we did not estimate LDL-C, HDL-C or triglycerides. This is one of the limitations of our study.

On the other hand, Tochigi et al. reported no significant relationship between development in symptoms of PTSD and serum cholesterol levels. This may be related to the long period (5 Years) after the event; together with the limited sample size (5 victims) might have affected the result.

Another principle finding of our research is a relation between increased serum cholesterol concentrations and verapamil therapy in PTSD patients. The present results offer an opportunity to gain insights as to the potential hypocholesterolemic action of verapamil and its use in psychiatric medicine. We found that verapamil showed a gradual but significant decline in symptom severity scores and serum cholesterol concentrations. These findings are in accordance with the study, in which Perez and his co-workers examined the effects of three calcium entry blockers (nifedipine, verapamil, and diltiazem) on serum biochemical parameters, aortic calcium and serum cholesterol concentrations of atherosclerotic egg-fed chickens. In this study, measurements of serum cholesterol concentration showed a highly significant decrease in verapamil group, while all calcium channel blockers had a tendency to decrease serum total cholesterol. Our results are very closely consistent with the research of Catalano et al., who compared verapamil with captopril and evaluated their effects on serum cholesterol levels, in hypertensive patients. Investigators noted significant total cholesterol reduction in verapamil group, while captopril showed only minor changes.

On the basis of findings of our research, we can say that high levels of serum cholesterol in PTSD are probably the consequence of the increased activity of the noradrenergic system, because there is strong correlation between noradrenalin and cholesterol level. The present findings are consistent with evidence that population with PTSD is at the high risk of stroke and

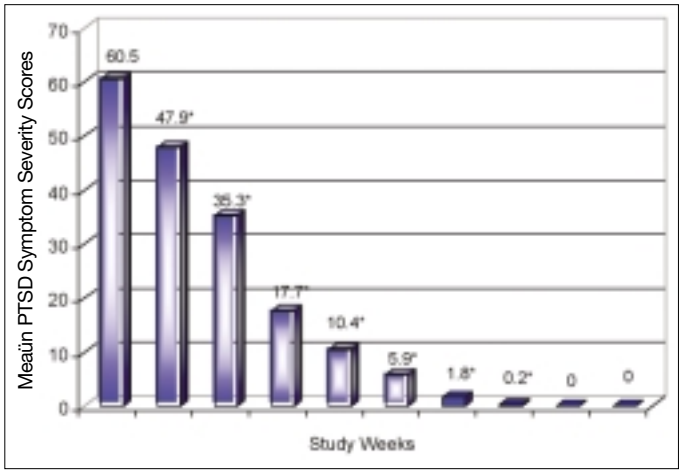

Figure 1. Effects of verapamil treatment on post traumatic stress disorder symptom severity scores

Numbers indicate the mean±SEM scores of 17 symptoms reports of all ratings in a total of 50 patients

*P<0.001 versus pre-treatment week-0

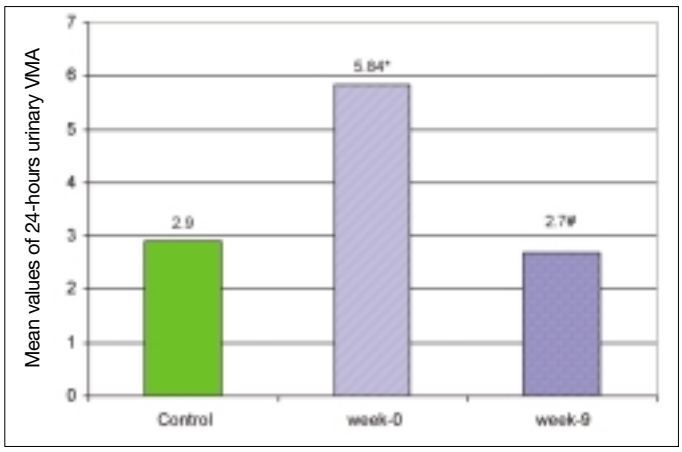

Figure 2. Effects of verapamil treatment on post 24-hours urinary VMA in post traumatic stress disorder patients

Mean values of 24-hours urinary VMA in 50 patients. Student's t-test comparing change in urinary VMA from normal subjects (Control group) to pretreatment week-0 and post treatment week-9.

* P<0.001 versus control group

Non significant versus control group

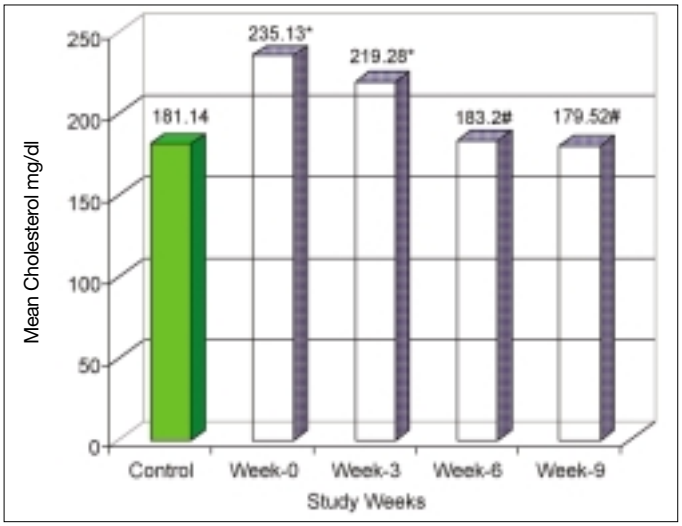

Figure 3. Effects of verapamil treatment on hypercholesterolemia in patients with post traumatic stress disorder

Numbers indicate the mean±SEM of total serum cholesterol in a total of 50 patients

* P<0.001 versus control group

Non significant versus control group

cardio-vascular disorders, because, the increase of serum cholesterol is directly related to the higher risk of arteriosclerosis and vascular accidents (22-24).

Moreover, verapamil therapy help to reduce the cardiovascular reactivity component of this disorder, thereby dampening overall risk to cardiovascular health. Indeed, this treatment outcome data shows serum cholesterol and cardiovascular reactivity diminishes with successful treatment of clusters of PTSD symptoms.

Conclusion

Verapamil have been reported as safe and effective treatment for high cholesterol levels in patients with PTSD. Moreover, drugs like Verapamil needs to be given the part of recovery program, which allows the brain to reestablish normal homeostatic changes and also decreases the cardiovascular risk factors.

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