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Original Article

CALCIUM CHANNEL BLOCKER VERAPAMIL: A NON OPIOID TREATMENT FOR ACUTE OPIOID ABSTINENCE SYNDROME

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ABSTRACT

Objective: Calcium ion plays an important role in acute opioid abstinence syndrome due to its effects on brain synaptosomes. Hence this study was conducted to observe the effects of calcium channel blocker Verapamil as a non-opioid treatment of acute opioid abstinence syndrome.

***Setting*:** Twenty healthy opiate-dependent patients seeking inpatient treatment were selected randomly. Verapamil 120mg/day was given in divided doses under single blind protocol. All patients completed the treatment program and stayed in the hospital for 10 days.

Results: Verapamil showed a gradual but highly significant improvement in signs and symptoms of acute opioid abstinence syndrome.

Conclusion: Verapamil was observed to be highly effective non-opioid treatment of acute opioid abstinence syndrome. Hence verapamil may be given extended clinical trial, because it did not show any adverse effect.

KEY WORDS: Opioid abstinence syndrome, verapamil, and calcium channel blocker.

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INTRODUCTION

To develop pharmacotherapy for opioid abstinence syndrome, several prerequisites for an ideal agent have been suggested. The primary site of action or specific receptor at which the drug acts and the molecular, biochemical and cellular events occurring in the abstinence syndrome i.e. molecular mechanisms in the tolerance, dependence and abstinence syndrome should be clearly understood. Rational pharmacotherapy will probably not be possible unless such mechanisms are understood in both pre-clinical and clinical settings.

Calcium plays an important role in action of opioids. There is clearly an inverse relationship between calcium and opiate activity. Opiates inhibit the depolarization induced influx of calcium into nerve terminals, there by reducing transmitter release. Thus calcium influx may be one of the mechanisms of the action of opioids, while the chronic administration of morphine produces an increase of calcium entry, associated with changes in calcium uptake and binding[1,2]. Uptake of calcium in to synaptosomes is greater and calcium levels in synaptosomes are elevated over controls.

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This increased content of calcium could reduce the inhibitory effects of opioids on neurotransmitter release, and finally resulting in tolerance[3,4].

Such increased content of calcium during precipitated withdrawal, resulting in increased neurotransmitter release and increased autonomic imbalance during the opioid abstinence syndrome[5]. The release of neurotransmitter is dependent on extracellular calcium and occurs when an action potential reaches the nerve terminal and it triggers sufficient influx of calcium ions. It has recently been shown that the calcium ions destabilizes the storage vesicles by interacting with a special protein, synaptotagmin associated with the vesicular membrane. Fusion of the vesicular membrane with the terminal membrane occurs, with the expulsion of neurotransmitter[6]. Increased density of calcium channel blocker binding sites has been observed, when the animals were treated with morphine, suggesting an increase in the number of calcium channels. So Verapamil a calcium channel antagonist by interacting with Ca channels, may suppress most of the signs and symptoms of abstinence syndrome by its central action[7,8]. Hence we planned the study to investigate the efficacy of Verapamil in hospitalized patients of acute opioid abstinence syndrome.

METHODS

This study was conducted in the department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center (JPMC), Karachi. The twenty selected opioid addicts who were seeking inpatient opioid abstinence treatment were enrolled and admitted to the inpatient psychiatry wards for 10 days. All patients were excluded who had a previous history of major psychiatric illness, current dependence on alcohol or other drugs of abuse like sedatives or hypnotics as well as cardiac and liver diseases. All of the patients were men and expressed interest in discontinuing use of opioids. All of the patients gave written consent to study that required an abrupt withdrawal from opioids after admission to the hospital. They were given a placebo capsules orally during day 1 and day 2 of admission to establish a baseline of symptoms and signs. They were observed and rated for the presence or absence of opioid withdrawal signs and symptoms expressed during the previous 24 hours by a trained observer. From day2 of admission, until discharge an observer completed the opiate withdrawal questionnaire (OWQ) which contained 20 typical symptoms and 6 opioid withdrawal signs[9]. Subjects indicated the degree to which they had experienced each symptom and same observer than rated the presence and intensity of signs on 5-point scale (Table-I)[5]. The composite score for observer rated signs and subjects reported

TABLE-I

Subjective symptoms and objective signs of acute opioid abstinence syndrome

No	*Symptoms*	*Signs*
1	Muscle cramps.	Lacrimation
2	Flushing	Rhinorrhea
3	Painful joints	Yawning
4	Yawning	Perspiration
5	Restlessness	Piloerection
6	Watery eyes	Rest lessness
7	Runny nose	
8	Chill or gooseflesh	
9	Sick to stomach	
10	Sneezing	
11	Abdominal cramps	
12	Irritability and tense	
13	Backache	
14	Sweating	
15	Depressed	
16	Trouble getting to sleep	
17	Shaky or tremulous	
18	Hot or cold flashes	
19	Bothered with noise	
20	Skin clammy and damp	

5-point scale of these symptoms and signs.

0 = not at all.
1 = a little.
2 = moderately.
3 = quite a bit.
4 = extremely.

symptoms was obtained by adding the scores from the individual items together. Urine samples were collected on day1, 5, and 10 of admission, and tested for opioids by using one-step dip and read chromatographic test strips. The amount of opioids in the urine was rated on 4-point scale (Table-II)[5]. All patients were at bed rest on day 2 and day 3 of admission. Thereafter from day 3 to day 9 of admission the patients received 40 mg of verapamil orally three times a day. All patients were discharged on day 10 of admission, when they were experiencing minimal or no withdrawal symptoms.

TABLE–II

Urine toxicology in opioid addicts treated with verapamil

No. of Patients	*Day1*	*Day5*	*Day10*
1	+3	+2	+1
2	+3	+2	0
3	+3	+2	+1
4	+3	+2	0
5	+3	+2	0
6	+3	+2	0
7	+2	+1	0
8	+2	+2	0
9	+3	+2	+1
10	+3	+2	0
11	+2	+1	0
12	+2	+1	0
13	+3	+2	0
14	+3	+2	+1
15	+2	+2	0
16	+3	+2	0
17	+3	+2	0
18	+3	+2	0
19	+2	+1	+1
20	+3	+2	0
Mean	2.8	1.8	0.2
SEM	0.09	0.09	0.09
P value		<.001	<.001

4 -Point scale of urine toxicology

0 = Nil
+1 = Traces.
+2 = >200ng / ml.
+3 = >1000ng / ml.

Statistical Analysis

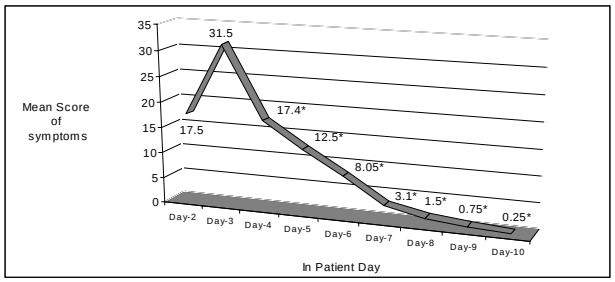
All data were expressed as means. Differences of mean symptoms score on various inpatient days were tested for significance by using the paired Student's t-test. For all analyses, P values less than 0.05 was considered significant.

RESULTS

Twenty opioid addicts who began the study, completed the therapy, and were discharged drug free. During study it was observed that all subjects were men ranging in age from 21-40 years ($\bar{x}$=29.1±1.3). They had a mean of 5.7 years history of opioid consumption (range 1-10 years). All patients had previous unsuccessful attempts at detoxifying from opiates and the mean number of previous supervised attempts to discontinue opioid was 2.25±0.19. All had subjective symptoms and objective signs of opiate withdrawal and urine specimens showing positive results when tested with front line opiates dipsticks. Diazepam 5mg for night time sedation and aspirin 300mg three times a day for muscle pain were used by 15 patients while hyosine 10mg a day was used by only three patients on days 3, 4, and 5 of hospitalization. A mean score of withdrawal symptoms 17.5±0.5 was obtained on day 2 of admission and increased to a peak of 31.5±0.6 during the baseline period that is on day 3 of admission. But after administration of Verapamil the withdrawal symptoms score decreased progressively from initial of 31.5±0.6 to 0.25± 0.09 on day 10 of admission (Fig. 1). Thus the effects of Verapamil to decrease the symptoms were highly significant (P<0.001) on day 4 to day 10 of admission as compared to the baseline effects in opioid addicts on day 3 of admission.

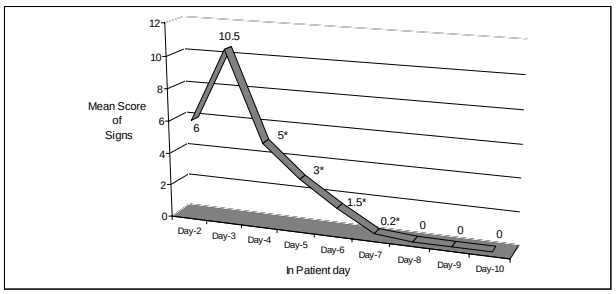
Similarly the relief of objective signs was also dramatic. A mean score of signs 6.0±0.2 was obtained on day 2 of admission, which increased to a peak of 10.5±0.2 during the baseline period that is on day 3 of admission. But after administration of verapamil the withdrawal signs score decreased progressively

Figure-1: Effects of verapamil treatment on subjective symptoms of acute withdrawal from opioids



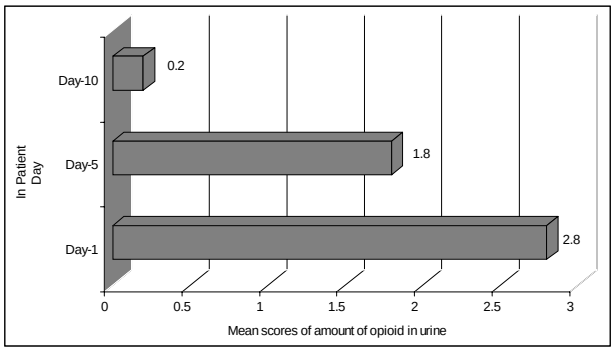
Number indicate mean scores of 20 symptoms reports in 20 patients from day two to day 10 of admission.
* P < 0.001 versus pretreatment in patient day 3.

Figure-2: Effects of verapamil treatment on objective signs of acute withdrawal from opioids



Number indicate mean scores of 6 signs in 20 patients from day one after admission to discharge on day 10.
* P < 0.001 versus pretreatment in patient day 3.

Figure-3: Amount of opioid in the urine of addicts treated with verapamil



Numbers indicate the mean scores of amount of opioid in urine in total of 20 patients, tested by using chromatographic test strips.

from initial of 10.5±0.2 to zero (0) on days 8, 9, and 10 of admission (Fig. 2). Thus the effects of verapamil to decrease the signs were highly significant (P<0.001) on day 4 to day 10 of admission as compared to baseline effects in opioid addicts on day 3 of admission.

While the urine toxicology was significantly and progressively decreased from the mean value of 2.8±0.09 on day 1 to 0.2±0.09 on day 10 of admission. Thus the effects of verapamil to excrete the opioid from body were highly significant (P<0.001) on day 5 and day 10 of admission as compared with day 1 of hospitalization.(Fig. 3)

DISCUSSION

Opiates acutely inhibit neuronal firing and hyperpolarize the membranes of most responsive cells. These effects are probably direct, and the result of altered membrane channel conductance or pump activity[9,10]. Calcium may act as second messenger to transmit opiate information into cells and initiate or inhibit cellular processes. Opiates inhibit the depolarization-induced influx of calcium into nerve terminals, thereby reducing neurotransmitter release. Increased density of calcium channel blocker binding sites has been observed in the brain, when the animals were treated chronically with morphine, suggesting an increase in the number of calcium channels[11,12]. Opioids reduce the calcium in the brain synaptosomes. Thus morphine decreases the binding of calcium to synaptic vesicles. This decrease in calcium binding sites of synaptic vesicles during opioid administration is consistent with evidence that synaptic vesicles are a major site of calcium accumulation during the development of tolerance and dependence. Such important redistribution of calcium is probably a key event for the neurochemical and behavioral expression of the opioid abstinence syndrome. So the drugs which have ability to modify the calcium fluxes, like Verapamil, reduce most of the signs and symptoms of opioid abstinence syndrome[13,14,15,9,2].

Calcium channel blocker Verapamil appear to inhibit, the withdrawal precipitated by naloxone in rat ileum. In morphine dependent rats, intraperitoneal administration of verapamil prevented diarrhoea and weight loss but not jumping observed during withdrawal. Administration of Verapamil, intracerebroventricularly, reduced the body weight loss and jumping response without modifying diarrhoea[3]. Thus both central and peripheral mechanisms are important in the inhibition of opioid abstinence syndrome by calcium channel blocker Verapamil.

CONCLUSION

In our study there is a clear pointer that Verapamil is effective and safe non-opioid treatment of acute opioid abstinence syndrome. This observation indicates that the redistributions of calcium are probably a key event for the expression of the opioid abstinence syndrome. However, the number of patients in our study is small. Hence verapamil must be given extended clinical trial, because it did not show any adverse effects.

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