Original Article

CALCIUM CHANNEL BLOCKER VERAPAMIL: A nonhormonal option for hot flashes management in patients with acute Opioid Abstinence Syndrome

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ABSTRACT

Objective: Given the problems associated with hormonal therapy, and the prominent problem of hot flashes, there is a need for nonhormonal agents to alleviate hot flashes. Calcium ions play an important role in brain synaptosomes. This study was conducted to investigate the efficacy of calcium channel blocker verapamil in hot flashes, the most frequently reported subjective symptom of acute opioid abstinence syndrome.

Methodology: The study was a 10 days single blind, random-assignment, inpatient trial for the patients of opioid abstinence syndrome with a very common symptom, the hot flashes. Twenty patients were given Verapamil, 120mg/ day in divided doses. All patients, who have completed the treatment program, stayed in the hospital for 10 days.

Results: Mean absolute change scores of number of hot flashes per day at endpoint, with baseline scores, showed a highly significant decline with verapamil treatment program.

Conclusion: The investigators found a benefit of verapamil in hot flashes.

KEY WORDS: Calcium Channel Blockers, Hot flashes, Norepinephrine, Verapamil.

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INTRODUCTION

Hot flashes are the most frequently reported symptom that occurs in the vast majority of patients with acute Opioid Abstinence Syndrome.[1] It is similar to a heat dissipation response and consists of sweating, cutaneous vasodilatation, increased heart rate and blood pressure.[2]

Hot flash seems to have behavioral and biochemical effects that involve interaction with catecholamine neurotransmitter systems and autonomic imbalance.[3,4] The demand for nonhormonal interventions for hot flashes is increasing because of the number of patients diagnosed with hormone-sensitive cancers and the hormone replacement therapy is not as beneficial as originally believed.[5,6]

Body temperature in homeotherms is regulated by the hypothalamus between upper thresholds for sweating and lower thresholds for shivering. Between these thresholds is a thermo neutral or null zone and the body temperature is regulated within these inter thresholds.[4,7] Norepinephrine plays an important role in thermoregulation mediated in the hypothalamus and much of the evidence of noradrenergic involvement has been derived from studies of locus coeruleus, which is the largest

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cluster of noradrenergic neurons in the brain and represents the primary source of noradrenergic innervations.[8,9]

Most recent studies have shown that increased brain norepinephrine levels in the patients with acute Opioid Abstinence Syndrome,[10,11] narrows the thermo neutral zone within which the thermoregulatory adjustments do not occur and most of the hot flashes are preceded by small but significant elevations in body temperature.[12,13] So hot flashes may be triggered when the body temperature exceeds the sweating threshold.[4,14,15] 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 in to nerve terminals, thereby 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. Uptake of calcium into synaptosomes is greater and calcium levels in synaptosomes are elevated over controls.[11] Such increased content of calcium during precipitated withdrawal, resulting in increased central sympathetic activation and autonomic imbalance,[10] which reduces the thermoneutral zone.[16]

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 destabilize 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.[17] Patients who are ineligible for or uncomfortable with hormone replacement therapy and who suffer from hot flashes that interfere with quality of life should be offered other regimens.[18] So by interacting with Ca channels verapamil may reduce the central sympathetic activity, widens the thermoneutral zone and ameliorates hot flashes. Hence we planned the study to investigate the efficacy of oral verapamil for the control of hot flashes in hospitalized patients of acute Opioid abstinence syndrome.

PATIENTS AND METHODS

The 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 psychiatric wards for 10 days. All patients 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 were excluded

All the patients were men, who expressed interest in discontinuing use of opioid and gave written consent to study that required an abrupt withdrawal from opioid, after admission to the hospital.

They were given a placebo capsules orally during day one and day two of admission to establish a baseline for frequency of hot flashes, a very common symptom of acute Opioid abstinence syndrome.

Patients indicated number and intensity of hot flashes per day to which they had experienced a symptom. The mean number of hot flashes per day reported was obtained by adding the scores from the individual patients together. All the patients were also assessed on the basis of physiological parameters, which include the systolic blood pressure, diastolic blood pressure and body temperature. Urine samples were collected on day 1, 5 and 10 of admission and tested for opioid by using one step dip and read chromatographic test strips. The amount of the opioid in urine was rated on 4-point scale (Table-I).[4,10,11] All patients were at bed rest on day two and day three of admission. There after from day 3 to day 9 of admission the patients received 40mg of verapamil orally three times a day. All patients completed the treatment program and were discharged on day 10 of admission.

Table-I: 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		<0.001	<0.001

4-Point scale of urine toxicology - The amount of opioid in urine of addict patient.
0 = No drug present in urine, +1 = Traces, +2 = >200ng/ml. +3 = >1000ng/ml.

Statistical Analysis: All data were expressed as means ± SEM. Differences of mean on various in patient 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 symptom free. During study it was observed that all subjects were men ranging in age from 21-40 years (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 hot flashes, a subjective symptom of acute opiate withdrawal and urine specimens showing positive results when tested with front line opiate dipsticks. The patients used no symptomatic therapy during the treatment days, which is day three to day nine of hospitalization. A mean number of hot flashes 7.2± 0.3 per day was obtained on day two of admission and increased to a peak of 18.9±0.2 during the base line pretreatment period that is on day three of admission. But after the administration of verapamil the hot flash frequency per day decreased progressively from initial of 18.9±0.2 to zero (0) on day 8, 9 and 10 of admission (Fig-1). Thus the effects of verapamil to decrease the frequency of hot flashes per day were highly significant (P< 0.001) on day 4 to day 10 of admission when

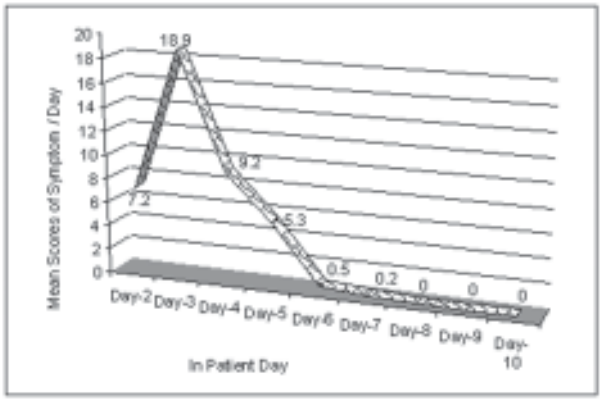

Fig-1: Effect of verapamil treatment on hot flashes Numbers indicate mean score of frequency of symptom per day reports in 20 patients did on each admission day.
* P < 0.001 versus pretreatment in patient day 3.

Table-II: Physiological parameters in patients treated with Verapamil

Physiological Parameters	*Day-3*	*Day-10*	*P-Value*
Mean Systolic Blood Pressure (mm of Hg)	115.7 ± 0.6	115.4 ± 0.1	N.S
Mean Diastolic Blood Pressure (mm of Hg)	71.3 ± 0.9	71.0 ± 0.7	N.S
Mean Temperature (°F)	98.8 ± 0.2	98.0 ± 0.1	P< 0.01 S

N= 20 S = Significant N.S = Not Significant

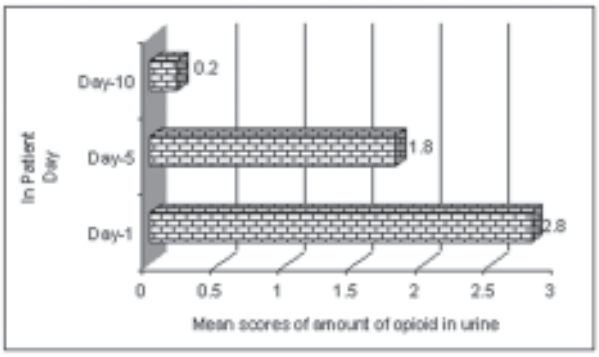

Fig-2: Amount of opioid in the urine of addicts treated with verapami l Numbers indicate the mean scores of amount of opioid in urine in total of 20 patients, tested by using chromatographic test strips.

compared to pretreatment baseline frequency of symptom on day 3 of admission.

There was no significant decrease in systolic and diastolic blood pressure. On the other hand, there was a small but statistically significant decrease in body temperature observed from day 3 to day 10 of admission (Table-II). The urine toxicology was significantly and progressively decreased from the mean value of 2.8±0.09 on day one to 1.8±0.09 on day 5 and 0.2±0.09 on day 10 of admission. Thus the effects of verapamil to excrete the opioid from body were also highly significant ($P < 0.001$) on day 5 and day 10 of admission as compared with the pretreatment day 1 of hospitalization (Fig-2).

DISCUSSION

Given the problems associated with hormonal therapy and the prominent problem of hot flashes, there is a need for nonhormonal agents to alleviate hot flashes. Hot flashes can impact on daily life functioning, particularly when they disrupt sleep leading to fatigue and irritability during the day.[5] Verapamil produced a rapid and statistically significant decrease in number of hot flashes that did occur (18.9 vs. 0). This study support the hypothesis that the central noradrenergic system are involved in the initiation of hot flashes and are consistent with the idea that central sympathetic activation and calcium dependent brain norepinephrine levels are elevated in this process.[3] The redistribution of calcium is probably a key event for the neurochemical and behavioral expression of hot flashes.

Most recent studies have shown that elevation of brain norepinephrine levels within hypothalamus narrows the width of thermoregulatory inter-threshold zone. This zone becomes so small as to be virtually non-existent and only small elevations in body temperature trigger hot flashes when the sweating threshold is crossed.[13-15]

Conversely, systemic administration of verapamil inhibits the firing of locus coeruleus noradrenergic cells by inhibiting the entry of calcium inside the cells and reduces norepinephrine release, which raises the sweating threshold, lowers the shivering threshold.[19] The drugs, which have an ability to modify the calcium fluxes, like verapamil, reduce the severity, intensity and ameliorate hot flashes.

These findings may be relevant to the effective use of verapamil in treatment of hot flashes. Further research must be done to assess the efficacy and safety of different nonhormonal pharmacological and herbal options for hot flashes management.

CONCLUSION

A nonhormonal agent verapamil yielded promising results in this study. This drug is well tolerated by all the patients. Thus, calcium channel blocker verapamil clearly does decrease hot flashes in patients with acute opioid abstinence syndrome. Well-designed large studies are needed to further explore new modalities of treatment.

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