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ROLE OF α-2 AGONIST CLONIDINE IN ATTENUATION OF HOT FLASHES IN PATIENTS WITH ACUTE OPIOID ABSTINENCE SYNDROME

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ABSTRACT

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. So this study was conducted to investigate the efficacy of Clonidine in hot flashes, the most frequently reported subjective symptom of acute opioid abstinence syndrome. The study was a 10 days single-blind, random-assignment, inpatient trial of Clonidine for patients of opioid abstinence syndrome with a very common symptom the hot flashes. 20 patients were given Clonidine 300 mcg/ day in divided doses. All patients, who have completed the treatment program, stayed in the hospital for 10 days. Mean absolute change scores of number of hot flashes per day at endpoint, with baseline scores, showed a very rapid and highly significant decline with Clonidine treatment program. The investigators found a benefit of Clonidine in hot flashes.

Keywords: Hot flashes, Norepinephrine and Clonidine.

INTRODUCTION

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 (Barton *et al.,* 2004, Sicat *et al.,* 2004). Hot flashes are the most frequently reported symptom and occur in the vast majority of patients with acute Opioid abstinence syndrome. It is similar to a heat dissipation response and consists of sweating, cutaneous vasodilatation, increased heart rate and blood pressure (Freedman *et al.,* 2001).

Hot flash seems to have behavioral and biochemical effects that involve interaction with catecholamine neurotransmitter systems and autonomic imbalance (Barton *et al.,* 2001).

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 (Zacny-1982).

Norepinephrine plays an important role in thermoregulation mediated in part through alpha-2 adrenergic receptors in the hypothalamus (Charney *et al.,* 1982). Much of the evidence of noradrenergic involvement has been derived from studies of locus coeruleus, which is the largest cluster of noradrenergic neurons in the brain and represents the primary source of noradrenergic innervations (Shanafelt *et al.,* 2002, Frishman 1995).

Most recent studies have shown that increased brain norepinephrine levels in the

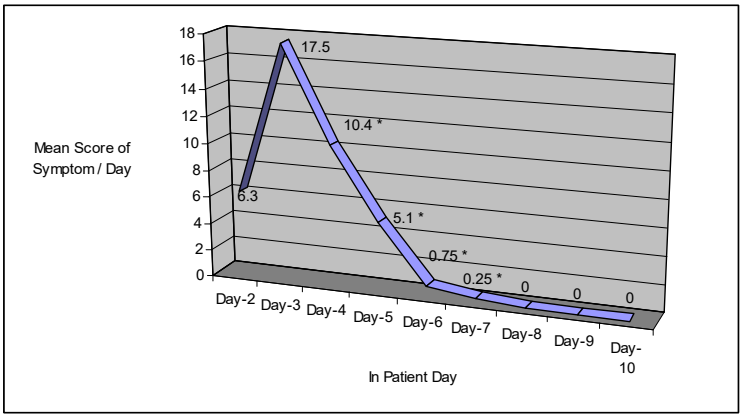

Fig. 1: Effect of Clonidine Treatment on Hot Flashes.
Numbers indicate mean score of frequency of symptom per day reports in 20 patients did on each admission day. *P<0.001 versus pretreatment in patient day 3.

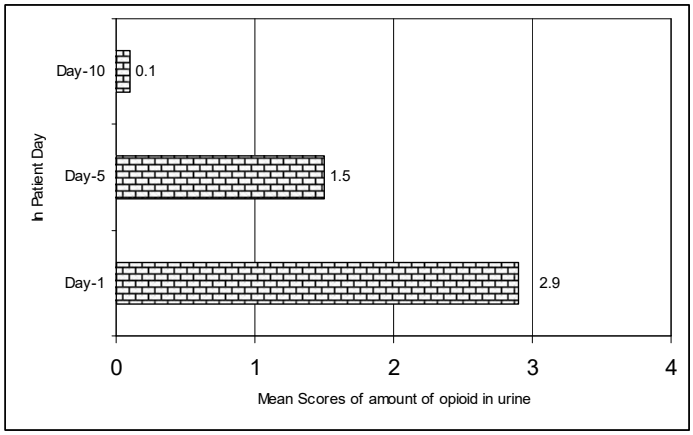

Fig. 2: Amount of Opioid in the Urine of Addicts treated with Clonidine
Numbers indicate the mean scores of amount of opioid in urine in total of 20 patients, tested by using chromatographic test strips.

patients with acute Opioid Abstinence Syndrome (Ansari *et al.,* 2001, Ansari *et al.,* 2003), 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 (Kronenberg 1994, Stearns *et al.,* 2002). So hot flashes may be triggered when the body temperature exceeds the sweating threshold (Mekjavic *et al.,* 1991, Brengelmann *et al.,* 1997).

Thus, norepinephrine and alpha-2 adrenoceptors, in the hypothalamus may be responsible for the events of hot flashes. Hence we planned the study to investigate the efficacy of oral Clonidine for the control of hot flashes in hospitalized patients of acute Opioid abstinence syndrome.

MATERIALS 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 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, 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 1 and day 2 of admission to establish a baseline for frequency of hot flashes, a very common symptom of acute Opioid abstinence syndrome.

Subjects indicated a number and intensity of hot flashes per day to which they had experience 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-1) (Ansari *et al.,* 2001). All patients were at bed rest on day 2 and day 3 of admission. There after from day 3 to day 9 of admission the patients received 150 mcg of Clonidine orally two times a day. All patients have completed the treatment program and were discharged on day 10 of admission.

STATISTICAL ANALYSIS

All data were expressed as means. Differences of mean 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.

Table 1
Urine Toxicology in Opioid Addicts treated with Clonidine

No. of Patients	Day 1	Day 5	Day 10
1	+3	+2	0
2	+3	+2	0
3	+3	+1	0
4	+3	+2	0
5	+3	+2	0
6	+3	+2	+1
7	+3	+1	0
8	+2	+2	0
9	+3	+2	0
10	+3	+1	0
11	+3	+2	0
12	+3	+1	+1
13	+3	+2	0
14	+3	+1	0
15	+2	+1	0
16	+3	+2	0
17	+3	+1	0
18	+3	+1	0
19	+3	+1	0
20	+3	+1	0
Mean	2.9	1.5	0.1
SEM	0.06	0.11	0.06
P value		<.001	<.001

4-Point Scale of Urine Toxicology
0 = Nil
+1 = Traces.
+2 = >200ng/ml.
+3 = >1000ng/ml.

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

Table 2
Physiological parameters in patients treated with Clonidine

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 Systolic Blood Pressure (mm of Hg)	71.3 ± 0.9	71.0 ± 0.7	N.S
Mean Temperature (^{o}F)	98.8 ± 0.2	98.0 ± 0.1	P< 0.01 S

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

subjective symptom of acute opiate with-drawal 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 3 to day 9 of hospitalization. A mean number of hot flashes 6.37 ± 0.5 per day was obtained on day 2 of admission and increased to a peak of 17.5 ± 0.09 during the base line pretreatment period that is on day 3 of admission. But after the administration of Clonidine the hot flash frequency per day decreased progressively from initial of 17.5 ± 0.09 to zero (0) on day 8, 9 and 10 of admission (Fig. 1). Thus the effects of Clonidine to decrease the frequency of hot flashes per day were highly significant (P< 0.001) on day 4 to day 10 of admission when compared to pretreatment baseline frequency of symptom on day 3 of admission.

While 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-2). The urine toxicology was significantly and progressively decreased from the mean value of 2.9 ± 0.06 on day 1 to 0.1 ± 0.06 on day 10 of admission. Thus the effects of Clonidine 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

Hot flashes are a significant problem for patients of acute opioid abstinence syndrome. Hot flashes can impact on daily life functioning, particularly when they disrupt sleep leading fatigue and irritability during the day (Barton *et al.,* 2004). Clonidine produced a rapid and statistically significant decrease in number of hot flashes that did occur (17.5 vs. 0). This study support the hypothesis that α-2 adrenergic receptors with in the central noradrenergic system are involved in the initiation of hot flashes and are consistent with the idea that central sympathetic activation and brain norepinephrine levels are elevated in this process (Barton *et al.,* 2001).

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 (Stearns *et al.,* 2002; Mekjavic *et al.,* 1991; Brengelmann *et al.,* 1997).

Conversely, systemic administration of Clonidine inhibits the firing of locus coeruleus noradrenergic cells and reduces nore-pinephrine release, which raises the sweating threshold, lowers the shivering threshold and ameliorates hot flashes (Zacny, 1982; Delaunay *et al.,* 1993; Kronenberg 1990).

So these findings may be relevant to the effective use of Clonidine in treatment of hot flashes. Although there is no research had been done to assess the efficacy or safety of different therapies of hot flashes. An immediate focus on some of the most

promising of these therapies could broaden the available treatment points and should provide new insights in to the mechanisms underlying hot flashes.

CONCLUSION

As the Clonidine has shown the effects and safety in the treatment of hot flashes, so it may be given an extended clinical trial in hospitalized patients because it did not show any adverse effects. Further research should be conducted to determine the complete physiological mechanism of this common symptom.

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