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ABSTINENCE SYNDROME ATTENUATING EFFECT OF HABBE SHIFA IN MORPHINE DEPENDENT RATS

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Abstract:

Withdrawal from morphine leads to the appearance of extreme anxiety accompanied of several physical disturbances, drug abuse and drug addiction form a spectrum of disorders that result in adverse consequences from the use of chemical substances. The study was carried out in either sex of Wistar rats 150-250 gm, all the animals was induced with administration of morphine s.c. for 7 days. The morphine dependent animals treated with Habbeshifa (Unani herbal compound formulation) extract and were assessed for various symptoms like writhing, squealing, teeth chattering, ptosis, wet dog type shaking, diarrhea, urination, grooming and piloerection. All the groups of animals were compared with NC. Test drug Habbeshifa produced significant degree of effects on morphine withdrawal syndrome and thus validated the Unani claim that Habbeshifa is an important drug to be useful in the management of opioid withdrawal.

Keywords:

Dependence; Withdrawal Symptoms; Naloxone Challenge; Opioid dependence; Habbeshifa.

Introduction

Substance use disorders is a brain disease that affects multiple brain circuits, including those involved in reward and motivation, learning and memory, and inhibitory control over behaviour¹. Substance use disorders are chronic relapsing conditions, leading to significant morbidity and impairment in psychosocial functioning^{2, 3}.

Drug abuse and drug addiction form a spectrum of disorders that result in adverse consequences from the use of chemical substances. Neuroadaptation underlies both the development of withdrawal symptoms and the specter of relapse⁴.

Addiction and dependence on opium has been related to the extreme cold *mizaj* (temperament) of it which when continued causes for craving of the drug in higher dose. The management of opium addiction has been centrally posited to slow and gradual reduction of opium dose or use of substitutes for opium that have lesser dependence or tolerance. A number of ways have been documented for efficient cure of the dependence. The serious problems that are encountered with the opium deaddiction are the severe withdrawal symptoms and the relapse of addiction. The success of the management lies in the extent of controlling the withdrawal symptoms during abstinence of opium⁵. Unani medicine has got a lot of single and compound drugs that have been successfully used to attenuate these symptoms. Experimental studies have also been carried out on *Jadwar (Delphinium denudatum Wall)*⁶, *Babuna (Matricariachamomilla)*⁷, *Fofal (Araca catechu)*⁸ for attenuation of withdrawal symptoms of opium abstinence. Management of substance use disorders has always been a challenge, with combinations of medications and psychosocial interventions being the main stay of treatment^{9, 10}.

Present study was undertaken to evaluate Unani claims of HabbeShifa for its use in opium de addiction. The models used were to assess the reduction in the behavioural symptoms using morphine dependent rats.

Materials and Methods

Animals:

The study was carried out in Wistar rats of sex, weighing 150-300 gm rats were kept in Animal House Facility, NIUM, Bangalore. They grouped and housed in polypropylene cages and maintained under good laboratory conditions (temperature $25 \pm 2^{\circ}\text{C}$, relative humidity 45-55 %) and given a standard pellet diet and water *ad libitum* under strict hygienic conditions. All the experiments involving animals were carried out according to CPCSEA guidelines, after getting the approval of the Institutional Animal Ethics Committee of National Institute of Unani Medicine, Bangalore, Karnataka, India, under Reg. No. 953/C/106/CPCSEA.

Preparation of the extract of the test drug and dose

All the ingredients of the test drug HabbeShifa (HS) were procured from the local market of Bangalore. The identity of the crude drugs was confirmed by authorized committee constituted by NIUM. A voucher specimen of the ingredients (No. 4462) has been deposited in the laboratory for further reference. The procured drugs were ground in an electric grinder to make a coarse powder. 100 gm of powder drug material was extracted in 500 ml of hydro alcoholic solution (50/50 %) in soxhlets apparatus except Acacia gum. Gum Acacia is not soluble in alcohol; therefore 1 % freshly prepared suspension of Acacia gum was mixed with hydro alcoholic extract prior to the

administration to the animals. It was continuously heated at boiling temperature for 6 hours. The extract was filtered and evaporated on water bath till it dried. The yield of hydro alcoholic extract of HS was found to be 20%.

The dose of the test drug (extract of HS) for Wistar rats were calculated by multiplying the human therapeutic dose of the test drug as described in Unani literature by conversion factor of 7¹¹, and were found to be 30 mg/kg b. w. for Wistar rats. Extracts of test drug were given by oral route with the help of canula, as this is the route of choice of drug administration in Unani system of medicine. Drug and vehicle were given in the form of suspension, freshly prepared at the time of administration to the animals.

Induction of morphine dependence in rats

To develop morphine dependence, rats were injected subcutaneously with morphine twice daily for 7 days. The dose of morphine on days 1 and 2 was 2.5 mg/kg; this dose was doubled every day thereafter to reach on day 6 a total dose of 40 mg/kg. On day 7, the animals received the last injection of morphine 50 mg/kg¹².

Group's allocation

The morphine dependent rats were divided into five groups of six animals each. The animals of group I served as negative control (NC) group and treated with 1 ml normal saline along with morphine as described above, group II and III (HS A and HS B) treated with single dose of Habbeshifa extract on the day 7, and group IV and V (HS CA and HS CB) treated with Habbeshifa extract daily twice with morphine.

Statistical analysis

The data obtained in different groups were statistically analyzed by using appropriate tests for variance analysis, $p < 0.05$ will be considered as significant.

Induction of withdrawal syndrome and treatment of habbeshifa extract in rats

Animals of all group received intraperitoneally 3 mg/kg naloxone 4 h after the last injection of morphine on seventh day of morphine treatment. Immediately after naloxone injection, each animal was placed in a transparent acrylic cylinder to observe the frequency of withdrawal manifestations for 30 minutes¹².

A single dose of Habbeshifa extract at 30 mg/kg and 60 mg/kg orally was given in group 2 and 3 respectively with morphine on day 7, and group 4 and 5 was given same dose respectively concurrently with morphine, twice daily for 6 days; and on day 7, the animals received the last dose of Habbeshifa extract with morphine 4 h before the naloxone challenge. The effect of Habbeshifa extract on the development of morphine dependence was assessed by comparing the frequency of behavioural abstinence manifestations of animals.

Observations and Results: The effect of extract of HS was observed on the withdrawal symptoms in morphine dependent rats by the method of Romandini et al.¹² This method although has subjective elements as various parameters are assessed simply by observation, however it has been widely considered suitable for preliminary study. The animals were assessed for various symptoms like writhing, squealing, teeth chattering, ptosis, wet dog type shaking, urination, grooming, and piloerection. Results are summarized in table and fig.

Table: Effect of Habbeshifa on withdrawal symptoms in morphine dependent rats.

Groups	N C	HS A	HS B	HS CA	HS CB
Writhing	6.5±0.34 [7(5, 7)]	2.5±0.5 [3(1, 4)]	0.83±0.40** [0.5(0, 2)]	2±0.93 [1.5(0, 6)]	0.33±0.22*** [0(0, 1)]
Squealing	6.66±1.49 [6(3, 11)]	0.33±0.21* [0(0, 1)]	0.5±0.22* [0.5(0, 1)]	0.33±0.33** [0(0, 2)]	0.33±0.21* [0(0, 1)]
Diarrhoea	3.66±0.61 [4(2, 5)]	2.33±0.42 [3(1, 3)]	0.33±0.33** [0(0, 2)]	2±0.77 [1.5(0, 5)]	1.03±0.42 [2(0, 2)]
Teeth Chat- tering	10.33±2.64 [10(3, 22)]	6.33±1.64 [6.5(2, 10)]	3.33±0.76 [3(2, 7)]	2.5±0.99* [2(0, 7)]	3.5±0.92 [3.5(1, 6)]
Grooming	10±1.15 [10(6, 14)]	7.66±0.98 [8(4, 11)]	6.66±1.38 [7(3, 12)]	8.5±0.92 [8.5(6, 11)]	4.66±1.05* [4(2, 9)]
Body shaking	2.5±0.42 [2.5(1, 4)]	1.66±0.61 [2(0, 3)]	0.5±0.36 [0(0, 2)]	4±1.77 [3(0, 10)]	0.66±0.21 [1(0, 1)]
Urination	1.83±0.30 [2(1, 3)]	1.66±0.33 [1.5(1, 3)]	0.83±0.40 [0.5(0, 2)]	0.33±0.21* [0(0, 1)]	0.83±0.30 [1(0, 2)]

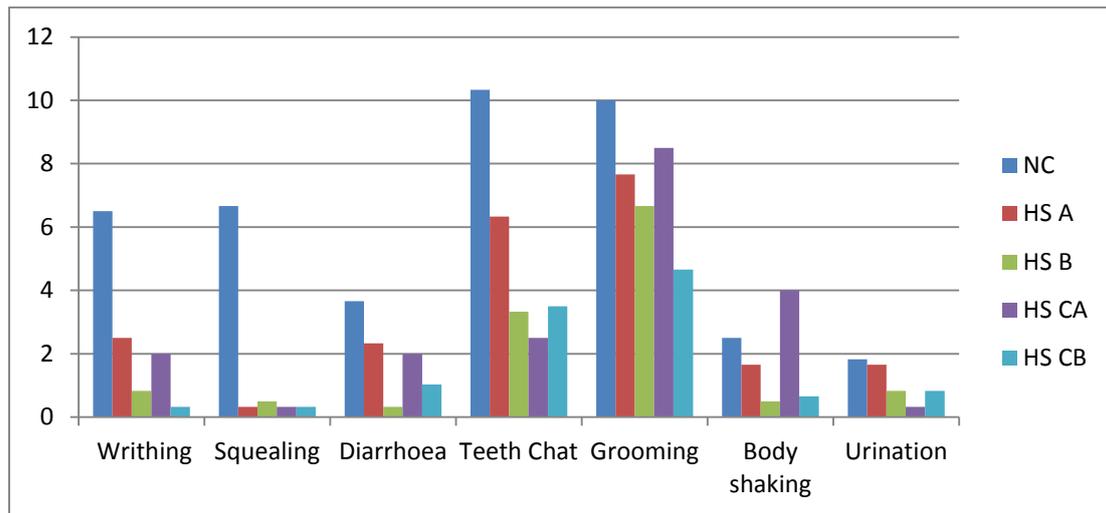


Fig: Effect of Habbeshifa on withdrawal symptoms in morphine dependent rats.

Discussion

Substance use disorders are chronic relapsing conditions, leading to significant morbidity and impairment in psychosocial functioning^{2,3}, management of substance use disorders has always been a challenge, with combinations of medications and psychosocial interventions being the main stay of treatment^{9,10}.

The study was conducted to evaluate the ability of HS to suppress the signs of withdrawal in morphine dependent rats. Administration of morphine in increasing doses caused development of severe dependence, which was confirmed by observing withdrawal signs after 4 h of the last dose of morphine in rats precipitated after naloxone challenge.

A reduction in the severity of the abstinence syndrome was observed in groups of animal treated with hydro alcoholic extract of HS along with morphine in different dose regimens. The significant reduction in withdrawal signs was observed in all groups of rats. Writhing, squealing, teeth chattering, ptosis, wet dog type shaking, urination, grooming and piloerection in rats were significantly decreased ($p < 0.05$) as compared to negative control.

Daturastramonium is main ingredient of HS contains a variety of alkaloids including atropine, hyoscamine and scopolamine that can all cause anticholinergic poisoning if taken in large concentrations¹³; however, it is also these anticholinergic alkaloids that contribute to the anti-asthmatic properties and it is therefore classified as a plant with anticholinergic properties¹⁴. Atropine is found to have more exciting properties, while scopolamine has more relaxing and hallucinogenic properties¹⁵. These compounds inhibit or block the physiological action of acetylcholine at a receptor site, and specifically at the muscarinic receptor¹⁶.

HS is a polyherbal pharmacopoeal dosage formulation used frequently in the treatment of headache, fatigue, malaise, periodic fever etc. In this study, we found that co-administration of HabbeShifa extract with morphine greatly attenuated the development of dependence. Moreover, administration of HS extract before induction of withdrawal syndrome by naloxone injection inhibited the expression of abstinence syndrome in morphine dependent animals. These findings indicate that HS has the ability to reduce both the development of dependence and expression of abstinence syndrome. cAMP pathway is known to be an important accompaniment to morphine dependence and plasma cAMP level is considered to be a sensitive index of dependence to morphine¹⁷.

It was observed that both the chronic co-administration of HS extract with morphine and the acute administration of HS extract before the induction of withdrawal syndrome blocked naloxone precipitated morphine withdrawal syndrome in morphine dependent animals. The exact sites and mechanism of action of HS needs further evaluation. The extract seems to have a rapid onset and long duration of action as evident from the results of all groups.

Conclusion

The present study was designed to evaluate the effects on morphine withdrawal syndrome of 50% alcoholic extract of HS in experimental models. Thus, its effect on symptoms determines the pharmacological effect produced by the test drug, along with the likely mechanism of action. The effect produced by the two doses of the test drug was compared with the negative control using appropriate statistical measures.

From the present study it may be inferred that the test drug attenuated to a significant degree the behavioral manifestations of morphine withdrawal syndrome. This study validates the claims of Unani physicians like Akbar Arzani, Azam Khan, M. Kabiruddin and others regarding the clinical use of HabbeShifa in the addiction of opium.

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