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Research Article

Evaluation of an anti-diuretic activity of fluvoxamine in albino rats

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ABSTRACT

Background: Diabetes insipidus is a disease characterized by high amounts of urine excretion. Antidiuretic drugs are used to treat this condition. Hence, our study intends to evaluate the anti-diuretic effect of fluvoxamine, a selective serotonin reuptake inhibitors in albino rats.
Methods: Albino rats were divided into three groups of six animals each. The control group was fed with distilled water 10 ml/kg body weight, standard group received 4 units of vasopressin and test group received fluvoxamine 18 mg/kg body weight. On the day of experiment, diuresis was induced in all the groups by giving frusemide in a dose of 20 mg/kg body weight after loading with saline at 25 ml/kg body weight. The animals were confined in diuretic cage for a period of 5 hrs and urine output was noted. Urine was analyzed for electrolyte concentration (Na^+, K^+, Cl−).
Results: There was significant reduction in urine output in the test group of animals when compared to the control group. Electrolyte concentration revealed relatively concentrated urine when compared to the control group.
Conclusions: Fluvoxamine has a significant anti-diuretic action in the albino rats.

Keywords: Anti-diuretic, Fluvoxamine, Albino rats, Diuretic cage

INTRODUCTION

Precise regulation of body fluid osmolality is essential. It is controlled by a finely tuned, intricate homeostatic mechanism that operates by adjusting both the rate of water intake and the rate of solute-free water excretion by the kidney, i.e., water balance. Abnormalities in this homeostatic system can result from genetic diseases, acquired diseases, or drugs and may cause serious and potentially life-threatening deviations in plasma osmolality.[1]

Anti-diuretic hormone (ADH) released from posterior pituitary has a crucial role in the control of water content of the body through its actions on the cells of the distal part of nephron and collecting tubules in the kidney. One of the main stimulus to ADH release is an increase in plasma osmolality which produces a sensation of thirst. A decrease in circulating blood volume, i.e., hypovolemia is another stimulus and here the stimuli arise from baroreceptors in cardiovascular system or from angiotensin release. ADH binds to the V_2 receptors in basolateral membrane of cells of distal tubule and collecting ducts of the nephron. Its main effect in collecting duct is to increase the rate of insertion of water channels into luminal membrane thus increasing the permeability of membrane to water thereby leading to water reabsorption from the nephron. Several drugs affect the action of ADH.

Diabetes insipidus (DI) is either due to deficient secretion of arginine vasopressin (AVP), also known as ADH by the pituitary gland (central DI) or due to renal tubular unresponsiveness to AVP (nephrogenic DI). This leads to polyuria, polydipsia with hyposthenuria, causing dehydration and hypernatremia if the patient is deprived of water.[2]

Vasopressin acts as an anti-diuretic by reabsorbing water via the principle cells of collecting ducts and the thick ascending loop of Henle, thereby increasing the plasma blood volume and decreasing the plasma osmolality.[3]

Case report has shown hyponatremia due to syndrome of inappropriate ADH associated with fluoxetine, paroxetine, fluvoxamine, escitalopram, and citalopram in the elderly which improved with discontinuation of the drugs and fluid restriction.[4]

Serotonin is a potential stimulator of ADH secretion. The selective serotonin reuptake inhibitors (SSRIs) are known to block the reuptake of serotonin in the central nervous system. Thus, inappropriate secretion or enhanced action of ADH as a result of enhanced serotonergic tone may contribute to the development of SSRI-induced hyponatremia.[5]

There is increase in aquaporin 2 (AQP2) expressions in the inner medullary collecting duct (IMCD) cells. This shows direct effect of the fluvoxamine in the IMCD which could explain the hyponatremia.[6]

The SSRIs are now the first choice of drugs for obsessive-compulsive disorder, panic disorder, social phobia, and post-traumatic stress disorder. Fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram are various SSRIs.[7]

This study has evaluated the effect of fluvoxamine as an anti-diuretic drug in albino Wistar rats. We hypothesize that this particular action of anti-diuresis can be due to:

- Secretion of ADH
- Direct renal effect of the drug by increasing in AQP2 expression in the IMCD cells of kidneys.

METHODS

The experiment has been conducted after obtaining permission from Institutional Animal Ethics Committee.

Albino rats from central animal house bearing registration number: 261/PO/bc/2000/CPCSEA Dated: 16/10/2012 of J.S.S. Medical College, Mysore was selected for the study.

Inclusion criteria

Rats that weighed 150-200 g of either sex, aged around 3-4 months, healthy with normal behavior and activity were selected for the study.

Exclusion criteria

- Pregnant rats
- Diseased rats.

The animals were divided into three groups each containing six animals. The first group was constituted by the control group receiving 10 ml/kg body weight of distilled water orally. The second was the standard group which received vasopressin 4 units/kg by intraperitoneal injection. The third group was constituted by the test group which received the test drug fluvoxamine 18 mg/kg body weight orally. The test drug was given for a period of 5 days.

On the 5th day, 1 hr after administration of respective drugs in the different groups, diuresis was induced in all groups of animals by furosemide 20 mg/kg after loading them with normal saline 25 ml/kg after overnight fasting.[8] The animals were kept in diuretic cage specially designed to separate faeces and urine at room temperature. The volume of urine collected was measured at the end of 5 hrs from each of the group along with sodium, potassium and chloride concentrations. One-way ANOVA method of analysis was used to compute the results.

RESULTS

There was a significant reduction in the average urine produced in the test group when compared to the control group though the volume of urine excreted in the test group was more than that of standard drug vasopressin group as mentioned in Table 1. The urine volume was just 50% in the test group when compared to the control group whereas it was 2.5 times more when compared to the standard group. The findings are suggestive of a moderate efficacy of fluvoxamine as an anti-diuretic drug.

Based on the electrolytes the urine sample of test group was concentrated when compared to the control group but it was less concentrated when compared to the standard group. The levels of electrolytes basically suggest water retention capacity of fluvoxamine leading to concentrated urine as indicated in Table 2.

The results were analyzed by one-way ANOVA method. The p value for urine volume excretion when compared between control and test was <0.05 signifying considerable anti-diuretic activity.

DISCUSSION

The above-mentioned results confirm the anti-diuretic action of fluvoxamine. The effect most probably is due to secretion of ADH and direct renal effect of the drug by increasing in AQP2 expression in the IMCD cells of kidneys. There is no much effect on salt excretion though which is reflected in the high urinary concentration of electrolytes to compensate for reduction in urine output.

CONCLUSION

Our study shows the anti-diuretic action of fluvoxamine in animal models of drug experimentation for anti-diuretic effect of drugs. Fluvoxamine has shown a considerable anti-diuretic action in a test group of albino Wistar rats when compared to control group of animals. Further studies are required to conclude the potency of fluvoxamine as the anti-diuretic drug before it can be used in human subjects.

Table 1: Urine volume in different groups of experimental animals.

Groups	Dose	Mean urine volume (ml)	Percentage volume in terms of control group	Percentage volume in terms of standard group
Control: Distilled water	5 ml/kg	5±0.17	100	500
Standard: Vasopressin	4 units i.p	1.0±0.25	20	100
Test: Fluvoxamine	18 mg/kg	2.5±0.30	50	250

Table 2: Electrolyte concentration in various groups.

Groups	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)
Control: Distilled water	120±2.5	23.7±1.1	110±1.8
Standard: Vasopressin	246±3.2	36.8±0.9	234±2.7
Test: Fluvoxamine	180±2.8	28±0.8	156±2.6

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Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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