EVALUATION OF ANTI-DIURETIC ACTIVITY OF FLUOXETINE IN ALBINO WISTAR RATS.

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ABSTRACT

Aim: To evaluate Fluoxetine for its antidiuretic activity in albino wistar rats. Introduction: An intricate set of mechanisms sense, signal and modulate changes in plasma volume. Any abnormalities in this physiological system, resulting from various genetic or acquired disorders, including certain drugs can alter the normal homeostatic mechanisms. Diabetes insipidus is one such disease, caused by the inability to conserve water and maintain an optimum free water level. Anti diuretic drugs are required to treat this condition. Most of the available drugs need some amount of circulating ADH for their action. Hence there is need for the drugs which have ADH independent mechanisms for conservation of plasma osmolality. Materials & Methods: Albino wistar rats were divided into 3 groups containing 6 animals each. Standard group received vasopressin (4 units intraperitoneally), control group received distilled water (10ml/kg body weight) and test group received fluoxetine (4.5mg/kg body weight). The test drug was given for a period of five days. On fifth day diuresis was induced in all the groups of animals by giving frusemide(20mg/kg body weight). Urine volume and electrolyte concentration was measured at the end of 5 hour observation period. Results & Discussion: The results suggested no significant anti diuretic activity of the test drug fluoxetine. Further tests are required to evaluate the antidiuretic activity of fluoxetine in humans if any.

KEYWORDS: Fluoxetine, Anti diuretic, diuretic cage.
INTRODUCTION
An intricate set of mechanisms sense, signal and modulate changes in plasma volume. The integrated result of these signalling mechanisms is to alter vascular tone and to regulate excretion and re-absorption of sodium by kidneys. The maintenance of water balance in healthy humans is principally accomplished through three interrelated determinants: thirst, Anti-diuretic hormone (ADH)/AVP and the kidneys. ADH is the primary determinant of free water excretion in the body. Its main target is the kidney, where it acts by altering the water permeability of the cortical and medullary collecting tubules. Water is reabsorbed by osmotic equilibration with the hypertonic interstitium and returned to the systemic circulation. Any abnormalities in this physiological system, resulting from various genetic or acquired disorders, including certain drugs can alter the normal homeostatic mechanisms\(^1\). These alterations can be life-threatening if not properly diagnosed and managed.

Diabetes insipidus is caused by the inability to conserve water and maintain an optimum free water level. The kidneys pass large amounts of dilute urine regardless of the body’s hydration state, leading to symptoms of extraordinary thirst, copious water intake, dry skin, and constipation. Diabetes Insipidus can result from two different etiological factors. Inadequate release of anti-diuretic hormone (ADH/AVP) from the hypothalamus is termed as Central Diabetes Insipidus. Inadequate response of the kidney to ADH is termed as Nephrogenic Diabetes Insipidus. Drugs like Amphotericin B, Colchicine, Demeclocycline, Gentamicin, Lithium, Loop diuretics, Methoxyflurane are also implicated in etiology of nephrogenic Diabetes Insipidus.\(^2\)

In patients with central DI, desmopressin is the drug of choice. Alternatives to desmopressin as pharmacologic therapy for DI include synthetic vasopressin and the non hormonal agents chlorpropamide, carbamazepine, clofibrate, thiazides and nonsteroidal anti-inflammatory drugs (NSAIDs).\(^2\) Most of the available drugs need some amount of circulating ADH for their action. Hence there is need for the drugs which have ADH independent mechanisms for conservation of plasma osmolality.

Selective Serotonin Reuptake Inhibitors (SSRIs) are the drugs indicated in the treatment of OCD, Panic disorders, anxiety disorders, PTSD and Premature Ejaculation.\(^3\) There are various Case Reports revealing the association of Hyponatremia with the use of selective serotonin reuptake inhibitors including Fluoxetine, Fluvoxamine, Sertaline, Paroxetine.\(^4\) The mechanism of SSRI induced hyponatremia is unclear. Some researchers attribute it to
Inappropriate secretion of Anti-diuretic hormone (SIADH) associated with the use of these drugs.

However, Fluoxetine, when studied in animal models, revealed increase in AQP2 protein abundance and water absorption in the intra-medullary collecting duct (IMCD), a mechanism independent of ADH secretion.\textsuperscript{[5]} In the present study we hypothesize that fluoxetine a commonly prescribed SSRI because of its capability of increasing AQP2 protein expression & ADH independent increase in re-absorption of water in intra-medullary collecting duct can be a therapeutic option in the treatment of disorders requiring anti-diuretic therapy particularly Central Diabetes Insipidus where there is deficiency of ADH.

**MATERIALS AND METHODS**

Animals for the study were obtained from central animal facility of J.S.S. MEDICAL COLLEGE, MYSORE. The study was conducted after being approved by Institutional Animal Ethical Committee.

**Inclusion Criteria**

Albino Wistar Rats of either sex, weighing 150-200 grams.

3-4 months of age.

Healthy rats with normal behaviour and activity.

**Exclusion Criteria**

Pregnant rats

Diseased rats.

The animals were divided into 3 groups each containing 6 animals. The first group was constituted by the control group receiving 10ml/kg body weight of distilled water. The second was the standard group which received vasopressin 4units/intra peritoneal injection. The third group was constituted by the test group which received the test drug fluoxetine 4.5 mg/kg/day. The test drug was given for a period of 5 days. On 5th day, one hour after administration of respective drugs in different groups, diuresis was induced in all groups of animals by Furosemide 20mg/kg after they were loaded with normal saline 25ml/kg after overnight fasting\textsuperscript{6}. 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 hours from each of the group along with sodium, potassium and chloride concentrations.
RESULTS & DISCUSSION

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
<th>Urine volume(ml)</th>
<th>% volume in terms of control group</th>
<th>% volume in terms of standard group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5ML/Kg</td>
<td>5±0.17</td>
<td>100%</td>
<td>500%</td>
</tr>
<tr>
<td>Vasopressin (standard)</td>
<td>4 units I.P</td>
<td>1.0±0.25</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Fluoxetine (test)</td>
<td>4.5mg/kg P.O</td>
<td>4.5±0.20</td>
<td>90%</td>
<td>450%</td>
</tr>
</tbody>
</table>

The urine volume for the different groups was measured at the end of 5 hours. The control group treated with distilled water, had average urine output of 5±0.17ml. The vasopressin treated standard group had average urine output of 1±0.25 ml. The test drug i.e fluoxetine treated group had average urine output of 4.5±0.2ml. The urine output in the test group was not significantly different from the control group. The finding may indicate no net effective anti-diuretic value of the test drug fluoxetine. The volume percentage in terms of control group considering it 100% was just 20% in the vasopressin/ standard group and it was 90% of the control value in the fluoxetine treated group. The volume percentage in terms of standard group considering it 100% was 500% in the control group and 450% in the fluoxetine treated group. The P value is thereby not significant when the control and the test groups are compared implying no or very little anti diuretic activity of the proposed drug fluoxetine.

ELECTROLYTE CONCENTRATION IN URINE

<table>
<thead>
<tr>
<th>Group</th>
<th>Na+ concentration mEq/l</th>
<th>K+ concentration mEq/l</th>
<th>Cl- concentration mEq/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>120 +/- 2.5</td>
<td>23.7 +/- 1.1</td>
<td>110 +/- 1.8</td>
</tr>
<tr>
<td>Vasopressin (standard)</td>
<td>246 +/- 3.2</td>
<td>36.8 +/- 0.9</td>
<td>234 +/- 2.7</td>
</tr>
<tr>
<td>Fluoxetine (test)</td>
<td>118 +/- 1.0</td>
<td>25.2 +/- 1.7</td>
<td>115 +/- 1.3</td>
</tr>
</tbody>
</table>

Vasopressin by virtue of its water retaining capacity produced concentrated urine. This was reflected in high loads of urinary electrolytes in the standard group. Na concentration in standard group was 246 mEq/L whereas it was similar in control and test groups at 120 and 118 mEq/L respectively. The K concentration in standard group was 36.8mEq/L whereas it was 23.7 and 25.2 mEq/L in control and test group respectively. The Cl concentration in the standard group was 234mEq/L whereas it was 110 and 115 mEq/l in control and test group respectively. The findings showing the urinary electrolytes corroborate the similar concentrations in test and control group and no net anti-diuretic activity in the fluoxetine treated group.
CONCLUSION
The study did not reveal any significant effect of fluoxetine on the volume of urine excreted in comparison to the control animals. It failed to establish the anti-diuretic effect of fluoxetine. However, further studies are required to evaluate the effect of fluoxetine and other SSRIs on fluid homeostasis and plasma osmolality to unravel the molecular mechanism behind well documented hyponatremia associated with their use.

REFERENCES