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Impact of Anxiolytic Therapy on Serum Electrolyte Balance in Menopausal Women

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ABSTRACT

The present study is designed to monitor the anxiolytic effects of diazepam (benzodiazepines) and its association with changes of serum electrolyte balance among forty (40) selected women within menopausal cycle. The experiment was carried out for four weeks and drug administrations were done orally. Serum electrolyte (sodium (Na^+), potassium (K^+), chloride ion (Cl^-) and Bicarbonate (CO_3) concentrations (mg/ml) experimented in the reproductive women showed differential changes in all the tested women orally administered with diazepams when compared with the control experiment (women not administered with the anxiolytic drug) during the four weeks of experiment. Na^+ and K^+ showed a concentration of 144 mg/ml and 4.1 mg/ml after seven days (week 1) of administrations and progressively decreases to 142.5 mg/ml and 4.1 mg/ml after 14 days (week 2) of administrations respectively. The concentration of Na^+ increased slightly to 143.4 mg/ml while K^+ maintained its initial concentration of 4.42 mg/ml after 28 days of administrations respectively. Cl^- and Bicarbonate (CO_3) ions showed a progressive increase in concentrations from day 7 to day 28 post administrations respectively. In all, serum electrolytes (sodium (Na^+), potassium (K^+) and chloride ion (Cl^-) showed slight increase in concentration when compared with the control experiment while Bicarbonate (CO_3) showed a non-significant reduction ($P>0.05$) in concentration when compared with the control experiment. Electrolytes are charged fluids present in the human body, and the balance of the electrolytes in our bodies is essential for normal function of our cells and our organs. Changes of electrolytes (fluid ions) are associated with stress-induced hypertension. Therefore it may be expected that diazepam and other anxiolytics elicit anxiolyte effects and decrease Systolic Blood Pressure (SBP) by changing electrolyte balance of the body system.

Keywords: Anxiolytics; Diazepams; Electrolytes; Menopausal women

INTRODUCTION

Anxiolytics

Diazepam and other benzodiazepines are xenobiotics used to reduce stress-induced anxiety [1]. In animals, benzodiazepines appear to act on parts of the limbic system to elicit calming effects [2]. At molecular level benzodiazepines elicit hyperpolarization by increasing the inhibitory effect of GABA [3]. These drugs also decrease the sympathetic activity [4]. Electrolytes are charged fluids present in the human body, and the balance of the electrolytes in our bodies is essential for normal function of our cells and our organs. Changes of electrolytes (fluid ions) are associated with stress-induced hypertension [5]. Therefore it may be expected that diazepam and other benzodiazepines elicit anxiolytic effects and decrease

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Systolic Blood Pressure (SBP) by changing electrolyte balance in the body system.

Anxiety and depression as identified by Lambert, et al. are among the most devastating health conditions especially in humans [6]. This could be attributed to factors ranging from personal to the economy state of an individual among others. Most clinical manifestations of these depressed physiologic conditions of the body are increased Systolic Blood Pressure (SBP) with elevated changes in the concentrations of electrolytes and steroidal hormones in the body system [7]. Continual increase of these blood pressures most often leads to the death of the brain cells (Ischemic stroke) [8]. Search for the best managements of anxiety and depressions in humans are paramount in recent days to avert these ugly incidents [9].Diazepam and other benzodiazepines are said to be one of the ligands at the GABA receptor which on binding at the appropriate subunits at the receptor of GABA brings about both physiologic and behavioral changes within the body of the said animal [10].

It is very important to elucidate the mechanisms and the varying effects of anxiolytic drug (benzodiazepines) interactions and their effects on both body electrolytes at the GABA receptor[11].

METHODS AND MATERIALS

Materials

All the reagents, equipment used in the present study were of analytical grade and products of BDH, May and Baker, Sigma Aldrich. The equipments are calibrated at each use.

Drug samples

A drug sample was used throughout the course of the study.

Diazepams: They were purchased locally in the form of ampoules (10 mg/2 ml) was injected orally at doses of 0.0046, 0.0036, 0.0026 and 0.0016 mg/kg. Control experiments were injected with normal saline (1 ml/kg).

Sample preparations

Each collected blood samples were centrifuged using the universal centrifuge at the speed of 200 g. The serums were stored in a clean sample bottle stored at the temperature of 4°C for further uses. SBP of the women were also noted 45 minutes post injection. Blood were collected in heparinized tubes for the analysis of serum electrolytes [12].

Analytical methods

Serum sodium, bicarbonates, chloride and potassium were estimated using an electrolyte analyzer which is a flame photometer (Corning 41°C) as described in Farooq, et al.

RESULTS

Statistical analysis

Data were reported as means ± SEM, where appropriate [13]. One-Way Analysis of Variance (ANOVA) and correlation analysis were used to analyze the experimental data and Duncan multiple test range was used to compare the group means obtained after each treatment with control measurements. Differences were considered significant when $P \leq 0.05$ (Table 1).

Variable	Week	Control	SD	Variable	Week	Experimental	Standard deviation
Sodium	WEEK 1	143.25	2.31455	Sodium	WEEK 1	144	2.31455
	WEEK 2	140.5556	2.06828		WEEK 2	142.5	2.06828
	WEEK 3	142.7778	2.10819		WEEK 3	142.75	2.10819
	WEEK 4	143.4444	3.50397		WEEK 4	145.5	3.50397
Potassium	WEEK 1	4.425	0.1669	Potassium	WEEK 1	4.4	0.1669
	WEEK 2	4.1333	0.15		WEEK 2	4.15	0.15
	WEEK 3	4.4	0.17321		WEEK 3	4.375	0.17321
	WEEK 4	4.4222	0.25386		WEEK 4	4.575	0.25386
Bicarbonate	WEEK 1	20.25	1.66905	Bicarbonate	WEEK 1	20.125	1.66905
	WEEK 2	23.4444	0.72648		WEEK 2	22.125	0.72648

	WEEK 3	21	1.5		WEEK 3	20.375	1.5
	WEEK 4	20.5556	2.18581		WEEK 4	20.375	2.18581
Chloride	WEEK 1	97.875	2.03101	Chloride	WEEK 1	98.5	2.03101
	WEEK 2	100	1.73205		WEEK 2	99.75	1.73205
	WEEK 3	95.3333	1.93649		WEEK 3	96.375	1.93649
	WEEK 4	99	1.73205		WEEK 4	99.125	1.73205

Note: Control, experimental=χ (mean) ± SD(standard deviation), variables=analysed serum electrolytes, week=period of experimental assays.

Table 1: The estimated flame photometer weekly wise experimental standard deviation.

Figure 1 show the changes associated with serum sodium concentrations in the analyzed samples from week one to the fourth week [14]. When compared with the control experiment and the corresponding weeks, the results were revealing and shows that the concentration of sodium in the experimental samples in week one differs significantly ($p<0.05$) from that on week four while its concentrations on the second week shows a statistical different ($p<0.05$) from that on week four [15]. The concentrations of sodium on week two and three shows no statistic different ($p>0.05$) from each other. When compared with the control experiments[16], sodium concentrations in week one, two and fourth week showed a statistic increase in concentrations when compared with the controlled experiments [17-19]. While its concentrations in week three reduced significantly when compared with the control experiments (Figure 2).

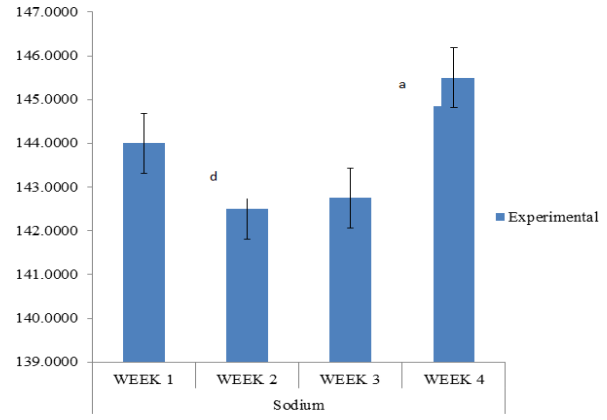


Figure 1: Sodium concentrations in the experimental samples from week one to four.

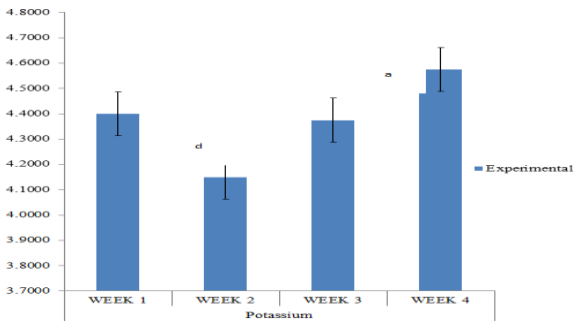


Figure 2: Potassium ions concentrations in the experimental samples from week one to four.

Serum bicarbonate ions concentration changes from week one to four of the studied period. Figure 3 show the changes associated with serum bicarbonates ions concentrations in the analyzed samples from week one to the fourth week [20]. When compared with the control experiment and the corresponding weeks [21], the results were revealing and shows that the concentration of bicarbonate ions in the experimental samples in week two differs significantly ($p<0.05$) from that on week one[22], three and four while its concentrations on week one, three and four shows no statistical different ($p>0.05$) from each other [23].

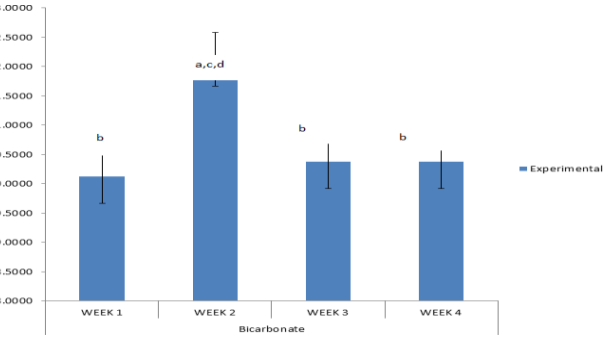


Figure 3: Bicarbonate ions concentrations in the experimental samples from week one to four.

Serum chloride ions Concentration changes from week one to four of the studied period. Figure 4 show the changes associated with serum chloride ions concentrations in the analyzed samples from week one to the fourth week [24]. When compared with the control experiment and the corresponding weeks[25], the results were revealing and shows that the concentration of chloride ions in the experimental samples in week three differs significantly ($p<0.05$) from that on week two and four while its concentrations on week one shows no statistical different ($p>0.05$) from the other weeks[26].

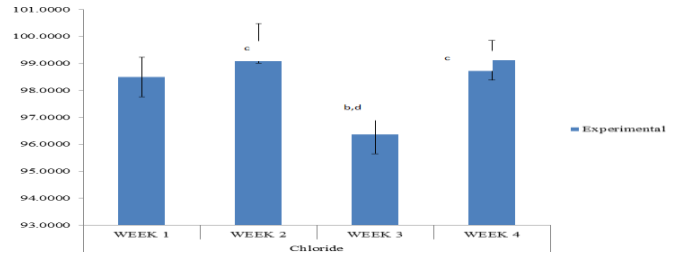


Figure 4: Bicarbonate ions concentrations in the experimental samples from week one to four.

DISCUSSION

Electrolytes are minerals found in bodily fluids that carry an electric charge and are essential to keeping the heart, nerves and muscles functioning properly [27]. As such, it is important to maintain a precise and constant balance of electrolytes to stay healthy [28]. The kidneys play an important role in ensuring that electrolyte levels remain invariant despite any changes the body may undergo. Having an excess or an insufficiency of electrolytes in the body can be dangerous and in some cases fatal [29].

Sodium an important intracellular fluid which is often implicated in the maintenance of fluid balances, pressures in the blood arterial walls is often secreted from its stores during depolarization conditions [30].This condition alters the resting potentials of the membrane and establishes action potentials on the body's internal membrane. In this study [31], diazepam effects on serum levels of sodium are very revealing [32]. Within the four weeks of study, sodium concentrations vary from each successive week to the other [33]. From the experimental data, it shows that sodium concentration in week one shows a significant variation at $p<0.05$ from week four and vice versa. Also sodium concentrations in week two shows a significant variation at $p<0.05$ from that on week four while the concentrations of sodium in week two and three shows no significant different ($p>0.05$) from each other [34].

It is clear to say that the concentrations of sodium from week one to the week four follows the decreasing order of: week four> week one > week two ≥ week three.

When compared with the control experiments [35], sodium shows higher serum concentrations in the experimental samples when treated with diazepam [36]. This also correlates with the results,which stated that the increases in sodium and potassium [37].

In this study serum sodium ion concentration shows significant increase ($p<0.05$) in concentration when compared with the control experiments in week one [38], two and four of the experimental groups. While its concentration decreases ($p>0.05$) in week three when compared with the control experiment of that week [39]. This decrease in week three could be attributed to a Smaller secretion of adrenal hormone may modify the membrane permeability for electrolytes to decrease intracellular Mg^{2+}/Ca^{2+} shift and thus may decrease the levels of calcium and sodium [40]. It could lead to the vasodilatation and reduction in systolic blood pressure.

Potassium is an important intracellular fluid ion involved in maintenance of fluid ion balance and also involved in Na/K gated ion channels movement during sympathetic conditions [41]. Within the four weeks of this study the following were observed as the order of potassium ions concentrations from the first week to the week four: week> week1 ≥ week 3> week2. It could be deduced from the data afore that serum potassium ion concentration in week four of the experimental sample shows a significant different ($p<0.05$) from that i.e serum potassium ion in week one [42]. While the concentration in week 2 differs significantly ($p<0.05$) from that in week four. It is seen that the concentrations of serum potassium in week one and three shows no significant different ($p>0.05$) from each other [43].

Serum potassium concentrations shows a markedly increase ($p<0.05$) in concentrations when compared with the control experiments in week two and four only [44]. It shows a no significant different ($p>0.05$) with the control experiments in week one while it shows a significant decrease in concentrations when compared with the control experiment in week three only[45]. This result also correlates with the findings of Farooq, et al. who reported that an increase in potassium ion [13], calcium and decreases in magnesium and SBP in rats treated with diazepam as observed in the present study are explainable in term of decrease in aldosterone and catecholamines in diazepam treated animals [46].

He went further to state that diazepam administration could decrease the activity of Hypothalamus Pituitary Adrenal axis (HPA) and secretion of aldosterone and catecholamines [47]. In a review compiled that serum electrolytes are often implicated in hypertensive cases which witnesses the influx of ions like Na, K inside the cells of the body [48].

They concluded that anti-anxiety drugs like diazepam induces hypnosis when bound at its receptors and this is characterized by high concentrations of electrolytes like Na, K, Ca in the blood serum.

Bicarbonates are blood gases mostly produced in the bile [49]. They serve buffers within the circulatory system resisting pH changes within the circulatory system. In this study, bicarbonate concentration found in the serum within the studied time shows some marked variations from each other [50].

From the results it is seen that the serum bicarbonate concentrations in week two of the studied time varied significantly ($p<0.05$) from that in week one, three and week four[51]. While it concentrations in week one shows no significant different ($p>0.05$) from week three and four, also the concentrations of serum bicarbonates in week three shows no significant different ($p>0.05$) from that in week one and four

[52]. Serum bicarbonate concentration in week four shows no significant different ($p>0.05$) from its concentrations in week one and week three [53]. When compared with the control experiment, bicarbonates showed a markedly decrease in concentrations in all the weeks under study. Bicarbonates play no crucial role in stress, anxiety and sympathetic cases [54]. Their major role in the body especially in the circulatory system is the maintenance of blood pH ranges.

Chloride ions are important electrolytes in the body whose major functions is the maintenance of osmotic fluid balance in the body [55]. They are as well involved during hyperpolarization reactions as a fluid ion. In this study chloride ion concentrations in the serum of the experimental samples were observed in all the studied periods and they show as well markedly variations from each of the studied period[56]. Chloride ion concentrations in week three shows a significant different ($p<0.05$) from its concentrations in week two and week four [57]. While the concentration in week two varies significantly ($p<0.05$) from the concentrations in week three[58], also its concentrations in week four varies significantly from that in week three[59]. Week one serum chloride ion concentrations shows no significant different ($p>0.05$) from the experimented groups in week two and four [60]. The order below shows the trend which they follow from week one to week four: week2 ≥ week4 ≥ week 1 > week 3.

When compared with the control experiments [61], it is seen clearly that chloride ion concentration in the serum of the experimented sample shows some degree of variations from the control experiments [62].

Serum chloride ions showed a significant increase ($p<0.05$) in concentrations in week one [63], three and the fourth week when compared with the standard [64]. While there is a sharp decrease ($p<0.05$) in concentrations of the ions in week two when as well compared with the standard [65]. Chloride are ions whose influx within the cell membranes result in hyperpolarization conditions and stabilization of the membrane resting potentials making it more negative [66].

This is an opposite gated pathway to depolarization mediated by Na/K ions in the membrane which often results to vaso-constrictions and an increase in SPB [67-70]. Lofgren stated that most anxiolytics induces inhibitory neurotransmitters e.g GABA, glycine etc [71]. The main effect of GABA is to stimulate the opening of a chloride channel [72], which allows chloride ions (Cl^-) to pass through the cell membrane and alter the electrochemical gradient [73]. This Cl^- ion flow into the neuron tends to stabilize the resting potential or make it more negative[74], which make it more difficult for an excitatory neurotransmitter to depolarize the membrane and generate an action potential. The total effect is inhibition[75], a reduction of neuronal activity [76]. GABA is released through exocytosis from the terminal boutons of the presynaptic neuron and stimulates the receptors on the postsynaptic neuron which opens Cl^- ion-channels[77-80]. There are three different types of receptors for GABA; the GABA-A, GABA-B and GABA-C receptors [81]. The GABA-A and GABA-C are ionotropic ligand gated Cl^-ion channels[82]. These receptors are quick to open their Cl^- channel [83-85]. The decrease in chloride ion concentration in week two of this study could be attributed to efflux of the ions from the membrane and restitution of the membrane potentials[86]. The GABA-B receptor is metabotropic and triggers a series of intracellular events which results in opening of ion channels.

CONCLUSION

Menopausal women are always associated with the use of stress reducing pharmaceutical products for calming effect either during their menstrual period or from their day to day activities. One of the risk influences of these xenobiotics is the action on serum electrolytes and steroidal hormones. Serum electrolyte concentrations in this group of women on diazepams increases as the week of induction progresses from 1 to 4.The molecular action of the xenobiotic is a confirmatory effect on the electrolytes.

AUTHOR'S CONTRIBUTIONS

Anikwe, Uchenna F: Conceived and designed the experiments, performed the experiment and processed the data, analyzed the data and wrote the manuscript.

Chukwudozie, Izuchukwu: Revised the manuscript and performed the experiment.

Brendan, Chibuike K: Performed the experiment and guided the experimental design.

Okenwa, Ezinne: Guided the experimental design and processed the data.

Oparaji, Emeka. H: Guided the experimental design, processed the data and wrote the manuscript.

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ETHICS

Authors declared no ethical issues that may arise after the publication of this manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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