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Water Balance and Serum Levels of Some Electrolytes in Oral Contraceptive-Treated Female Wistar Rats

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This study was designed to investigate the effect of combined oral contraceptive (OC) on water consumption, urinary output and serum levels of sodium, potassium and calcium. Twenty female rats were used. Rats were distributed into two groups, control and OC-treated groups, with ten rats in each group. OC-treated group took combined OC, containing 1.0 μg ethinyloestradiol and 10.0 μg norgestrel intragastrically for nine weeks. Both groups fed on standard rat chow and were allowed free access to water throughout the nine weeks of experiment. Water consumption and urinary output was noted and recorded during the experiment period. After the experiment period, rats were sacrificed and serum levels of sodium and potassium were determined in both groups using the flame photometry method, while serum calcium level was determined in both groups using cresolphthalein complexone. There was significant decrease in water consumption and urinary output. No significant differences were found in the mean serum levels of sodium, potassium and calcium.

Key words: Water consumption, urinary output, plasma electrolytes, oral contraceptive

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INTRODUCTION

Oral Contraceptive (OC) ingestion has been shown to influence body water balance and thermoregulation (Nadel, 1998). Earlier studies have also shown that OC administration decreases water consumption (Schwartz and Wade, 1981; Lobo *et al*., 1993; Kisley *et al*., 1999; Wallen *et al*., 2001), however, this is not in agreement with previous study of Gray and Wade (1981) which suggests that OC therapy increases water drinking. The hypodipsogenic effect of OC has been attributed to the direct effect of oestradiol on the hypothalamus (Gray and Wade, 1981; Flanagan-Cato *et al*., 1998). Estrogen administration has been demonstrated to cause attenuation of water intake in response to peripheral, intracerebroventricular administration of angiotensin II (ang II) as well as isoproterenol, a beta-adrenergic agonist that activates Rennin-Angiotensin System (RAS) (Findlay *et al*., 1979; Fregly, 1980). The attenuation of ang II-induced water drinking is centrally controlled and has been confirmed in several studies (Kisley *et al*., 1999).

OC administration has also been reported to affect serum electrolytes. Studies have indicated reduced serum concentration of calcium, magnesium and phosphorus (Simpson and Dale, 1972). This is not in consonance with some studies (Ghoneim *et al*., 1975). OC infusion has been reported to increase plasma levels of iron, transferrin, zinc and copper (Eric *et al*., 1979; Hatcher *et al*., 1994; Sheriff, 1999). Previous studies have also shown that OC therapy has no significant changes on serum sodium and potassium levels (Ghoneim *et al*., 1975).

However, none of these studies has associated the changes seen in serum electrolytes in OC therapy with water consumption and urinary output.

The aim of this study is to determine whether the use of combined OC causes changes in serum sodium, potassium and calcium levels and to investigate the association of the modulation of water consumption and urinary output with these changes.

MATERIALS AND METHODS

This study was carried out in the animal house of the Ladoke Akintola University of Technology, Ogbomoso, Oyo state, Nigeria. OC was administered daily between 07:00 and 08:00 h during the experimental period.

Twenty female wistar rats were used. They were distributed into two groups, the control and OC-treated groups, with ten rats in each group.

OC-treated group received combined OC containing 1.0 μg ethinyloestradiol and 10.0 μg norgestrel intragastrically for nine weeks. Throughout the period of experiment, both groups were allowed free access to standard rat chow and water.

Water consumption and urinary output were recorded daily throughout the nine weeks of experiment. Each rat was kept in a metabolic cage with a feeder, containing known volume of water, attached to it and a container below the metabolic cage that collected urine. After each day, the volume of water remaining in the feeder was deducted from the initial volume to obtain the average daily consumption of water per rat. Urine collected in the container below the metabolic cage was drawn into a syringe and measured to obtain the average daily urinary output per rat. After the ninth week of experiment, rats were sacrificed and blood was collected to determine serum levels of sodium, potassium and calcium in both groups. Serum sodium and potassium levels were determined using the flame photometry method (410 flame photometer-Chiron Diagnostics), following the manufacturers guidelines.

Statistical analyses were performed using SPSS windows version 10.0. Unpaired t-test was performed to evaluate the influence of OC on water consumption and serum sodium, potassium and calcium levels. Paired t-test was performed to evaluate the influence of OC on absolute and body weight-corrected values of water consumption and urinary output. $p<0.05$ was used as the significant level. Data are presented as Mean±Standard Error of Mean (SEM).

RESULTS AND DISCUSSION

Significant decrease in the intake of water was seen in the OC-treated group. This began in the 4th week of treatment and the decrease persisted throughout the experiment period when compared with the control group. The decrease in water intake was statistically significant in the 4th, 6th, 8th and 9th weeks of experiment (Fig. 1).

Water intake in OC-treated rats was significantly less than that of the control rats (Table 1). This persisted when water consumption was normalized to body weight (Table 2).

Urinary output was significantly less in OC-treated rats when compared with the control rats (21%) (Table 3). There was little increase in serum sodium and potassium levels in OC-treated rats. Serum calcium slightly decreased in OC-treated rats. However, these changes were not statistically significant (Table 4).

Table 1: Effect of OC on water consumption: absolute values

Values	Control	OC-treated
I (mL)	22.9±0.7	23.1±0.9
F (mL)	25.7±1.1	18.0±1.9*
Δ (%)	2.8 (12)	-5.1 (22)*

Data are as shown as Means±SEM I = Initial values, F = Final values, Δ : Changes, *$p<0.05$

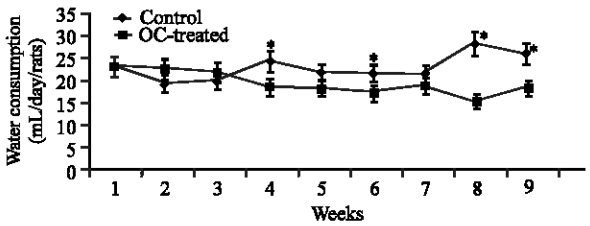

Fig. 1: Effect of combined oral contraceptive therapy on weekly water consumption

Table 2: Effect of OC on water consumption: body weight-corrected

Values	Control	OC-treated
I (mL)	20.5±3.8	21.0±3.0
F (mL)	14.1±4.0	11.6±5.8*
-Δ (%)	6.4 (31)	9.4 (45)*

Data are as shown as Mean±SEM. I = Initial values, F = Final values, Δ: Changes, *p<0.05

Table 3: Effect of OC on urinary output

Values	Control	OC-treated
I (mL)	2.7±0.4	2.8±0.3
F (mL)	3.1±0.5	2.2±0.2*
-Δ (%)	0.4 (15)	0.6 (21)*

Data are as shown as Means±SEM. I: Initial values, F = Final values, Δ: Changes, * p<0.05

Table 4: Effect of OC on some serum electrolytes

Serum electrolytes	Control	OC-treated
Serum sodium	136.5±1.40	138.70±1.10
Serum potassium	4.4±0.90	4.60±0.60
Serum calcium	1.3±0.04	1.02±0.08

Data are as shown as Mean±SEM. *p<0.05

Several studies have shown that OC infusion is associated with stimulation of RAS (Findlay *et al*., 1979; Fregly, 1980; Fowler *et al*., 1985; Krause *et al*., 2003), low water intake (Schwartz and Wade, 1981; Lobo *et al*., 1993; Kisley *et al*., 1999; Wallen *et al*., 2001) and fluctuation of serum electrolytes (Simpson and Dale, 1972; Ghoneim *et al*., 1975; Eric *et al*., 1979; Hatcher *et al*., 1994; Sheriff, 1999). However, none of these studies has observed the weekly changes in water consumption seen in OC therapy in association with urinary output, RAS activity and mean serum electrolytes. The novel findings of this study are the first to scientifically document the decrease in water consumption seen in OC therapy in association with RAS activation, urinary output and serum electrolytes balance.

Present finding that administration of a combination of OC steroids, ethinyloestradiol and norgestrel, decreases water intake was consistent with studies of Schwartz and Wade, which documents that OC therapy, is associated with low water intake. The reduction in water consumption seen in OC-treated rats became significant in the 4th week and persisted subsequently throughout the period of experiment when compared with the control group. This reduction persisted when water consumption was normalized with body weight. This could suggest that OC suppresses the thirst center in the brain, which modulates the drinking behaviour in OC-treated rats, abrogating the urge to take water. This suggests that the suppression of water intake and thirst caused by combined OC infusion overrides RAS-induced drinking.

This study also seems to be the first to document the effect of OC treatment on urinary output. Observations from this study showed that there was a reduction in urinary output in OC-treated rats. This decrease in water excretion suggests that OC stimulates RAS activity and thus increases plasma concentration of ang II, the effector substance of RAS, which acts on the kidneys to cause water and sodium reabsorption. This is in agreement with previous study of Fowler and Kisley. The result could also suggests that the reduction in water consumption activates RAS to cause a significant decrease in water excretion. However RAS could not activate the thirst centers in OC therapy. Since it is a known fact that oestrogens, like aldosterone, cause fluid retention, it may be that the anti-diuretic effect of OC is so powerful that the thirst reflex is suppressed.

This study also showed that there was a little increase in serum sodium and potassium levels, but a little decrease in serum calcium level in OC therapy. This changes were however not significant. This is in consonance with previous study of Ghoneim, which shows that serum levels of sodium and potassium increase during OC therapy, but serum calcium level decreases. This observation suggests that the insignificant changes seen in serum level of electrolytes in OC-treated rats could be as a result of the reabsorption of sodium from the renal tubules following the activation of RAS. This difference remained insignificant, because water was reabsorbed simultaneously with sodium reabsorption, conversely reducing water and sodium excretion caused by RAS activation.

CONCLUSION

This study shows that combined OC therapy significantly reduces water consumption and urinary output with no significant changes in the mean serum levels of sodium, potassium and calcium. The present study clearly documents the mechanism by which mean serum levels of sodium, potassium and calcium are maintained in OC therapy.

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