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Effect of Chronic Administration of Medroxyprogesterone (Depo-Provera) Contraceptive on Renal Functions in Female Wistar Rats

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ABSTRACT

Background: Medroxyprogesterone (Depo-Provera) is an injectable contraceptive used in preventing ovulation, and thus pregnancy. Progesterone used in oral contraceptives has been implicated in some renal diseases. Thus, Depo-Provera which is a form of progesterone that is associated with some adverse effects must be cautiously used. The study was carried out to investigate the effect of chronic administration of Depo-Provera on renal functions in female Wistar rats.

Methodology: Twenty-four female Wistar rats were randomly grouped into four groups of 6 rats each with group I as control. Group II was administered 2.14mg/kg (low dose), group III was administered 4.28mg/kg (moderate dose), and group IV was administered 8.56mg/kg (high dose) of Depo-Provera once. Weekly urine analysis was done throughout the three months of the study, following which the rats were euthanized, and blood samples collected for serum electrolytes, urea and creatinine.

Result: The moderate and high dose groups showed significant ($p < 0.05$) decrease in calcium, and significant ($p < 0.05$) increase in potassium, urea and creatinine levels. There was also significant ($p < 0.05$) decrease in

sodium of high dose, and significant ($p < 0.05$) increase in creatinine of low dose groups; however, there was no significant ($p > 0.05$) change in serum phosphate and chloride levels globally. The urinalysis results summarily showed protein was positive (+) with a pH of 5.5 in low dose group, while the moderate and high dose groups were positive for bilirubin (2+), and protein (3+) with a pH of 4.0.

Conclusion: Depo-Provera should be cautiously used to avoid renal dysfunction due to accumulation of urea and creatinine, and loss of bone mineral density which can predispose to osteoporosis.

Keywords: Creatinine, Medroxyprogesterone, Renal functions, Serum electrolytes

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INTRODUCTION

Medroxyprogesterone (Depo-Provera) is a form of progesterone, an injectable contraceptive used in preventing ovulation, and thus pregnancy. Due to its high efficacy, accessibility along with cost effectiveness and long duration of action, this method of contraception has been widely patronized by women in sub-Saharan Africa (1,2). Each vial (1ml) contains 150 mg of medroxyprogesterone acetate suspended in an aqueous solution (3). This standard dosage is given once every 3 months (13 weeks) via deep intramuscular (IM) injection, and reports have shown an effectiveness of 99% in women when administered as when due (4). Like any other drug, it is associated with some adverse effects that call for some level of caution (5,6). These effects may include premenstrual-like symptoms (bloating, fluid retention, mood changes); irregular menstrual periods; bruising and swelling of veins; among others (7).

Progesterone and oestradiol regulate majorly reproductive functions but do have effects on fluid-balance regulation. Low progestogen has been reported to influence shift in electrolytes concentration by resulting in mild fluid retention (8). Body fluid homeostasis, partly controlled by the renal system is achieved through the interplay between various electrolytes and hormones in the body. Progesterone used in oral contraceptives has been implicated in some renal diseases (8), thus, Depo-Provera which is a form of progesterone that is associated with its own attending adverse effects must be cautiously used. Creatinine, a breakdown product of creatine phosphate and muscle protein metabolism is synthesized in the liver and kidneys (9). It is removed from the

blood chiefly by the kidneys, primarily through glomerular filtration. Urea is a colourless, odourless solid, highly soluble in water (10,11). It serves an important role in the metabolism of nitrogen-containing compounds by animals. The body uses it in many physiologic processes, including excretion of nitrogen, and countercurrent system mechanism (12,13). Thus, a balance between the interactions of the various electrolytes in the body such as sodium, calcium, potassium, chlorine is important for normal body system functioning through renal reabsorption and secretion processes. Due to its indiscriminate use as contraceptive, the present study aimed at investigating the effect of Depo-Provera on renal functions in female Wistar rats.

Methodology

The study was carried out using 24 female Wistar rats weighing between 220-250g. They were randomly divided into 4 groups of 6 rats each. Group I served as control and was given 0.5ml/kg 0.9% NaCl once. Group II, III and IV were administered 2.14mg/kg (low dose), 4.28mg/kg (moderate dose) and 8.56mg/kg (high dose) of Depo-Provera intramuscularly once respectively which is comparable to corrected weight dose in humans. Urine sample was collected weekly for urinalysis throughout the 90 days of the study. At the end of the study period, the animals were euthanized under anaesthesia by injecting ketamine hydrochloride 50mg/Kg subcutaneously. Blood samples were collected from the heart into EDTA bottles and were centrifuged at 3000rpm for 15minutes ahead of electrolytes (sodium, potassium, calcium and chloride), urea and creatinine assay.

Animal grouping

Twenty-four (24) female rats weighing 220–250g were purchased

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from National Center for Research, Khartoum, Sudan. They were housed and maintained in the animal house of the Faculty of Veterinary Medicine, University of Khartoum, Shambat, Sudan. They were kept in metabolic cages with good ventilation, free access to standard rat pellet feeds and water ad libitum. The animals were subjected to artificial day and night cycle of 12 hours by 12 hours light and darkness, under optimum temperature of 25-30°C. The animals were acclimatized for two weeks prior to commencement of the study. The research protocols which were both invasive and non-invasive were approved by the Ethical Research Committee for Animal Experiments (IUA/ERC/2016A/1159) of the International University of Africa, Khartoum, and were conducted in accordance with internationally acceptable principle for laboratory animal use and care.

Statistical Analysis

Statistical analysis was done with the aid of the statistical package for social sciences (SPSS version 20). Differences in means were obtained using ANOVA test. All values reported in the study were expressed as MEAN±SEM (standard error of mean). Differences were taken to be significant at $P < 0.05$.

RESULTS

There was significant ($p < 0.05$) decrease in the level of sodium in the high dose but no significant ($p > 0.05$) changes were seen in the low and moderate doses as seen in Table 1. There was significant ($p < 0.05$) increase in potassium levels of moderate and high doses but no significant ($p > 0.05$) change was observed in low dose. There was significant ($p < 0.05$) reduction in calcium levels of moderate and high doses but no significant ($p > 0.05$) change was seen in low dose. There were no significant ($p > 0.05$) changes in phosphate and chloride levels of all the groups administered Depo-Provera. There was significant ($p < 0.05$) increase in the levels of urea in moderate and high doses but no significant ($p > 0.05$) change was seen in group administered low dose. There was significant ($p < 0.05$) increase in creatinine levels of all the groups administered Depo-Provera. The urinalysis results for the control and low dose groups summarily revealed that protein was positive (+) with a pH of 5.5, while the moderate and high dose groups reflected positive for bilirubin (2+), and protein (3+) with a pH of 4.0.

DISCUSSION

The study showed that plasma levels of electrolytes and urea assay of the low dose group were unremarkable and thus, favourably compete with the electrolytes and urea levels of the control group. In contrary, there was elevation in the creatinine level of rats administered low dose Depo-Provera. The rats administered moderate dose of Depo-Provera also showed derangements in the plasma levels of the electrolytes except in sodium, phosphate

and chloride levels that were not significantly different from the control. However, the urea and creatinine levels were remarkably elevated. In the high dose group, the study also revealed apart from serum phosphate and chloride levels, a global derangement in all the plasma levels of electrolytes, urea and creatinine. The level of chloride that was insignificant in the current study was consistent with the work of Hameed et al. (2001) (14). The sodium and calcium levels demonstrated hyponatraemia and hypocalcaemia respectively that were dose dependent, though only significant for sodium at moderate dose and significant for calcium at moderate and high doses. It was also observed that there was a dose dependent increase in the serum levels of potassium and urea, though only significant in moderate and high doses of Depo-Provera administration. There was also global creatinine elevation which was dose dependent even in the low dose which was seemingly favourably comparable with the control group. Clinically, it was also observed that there was generalized body swelling, decreased urinary output, and overall inactivity perhaps due to inability of the kidneys to remove waste and balance body fluids in the moderate and high dose Depo-Provera administered rats. This could have arisen from renal insult altering tubular functions as seen by increased urea and creatinine levels, while the protein leakage perhaps was due to glomerular damage provoked by the heavy dose of the Depo-Provera as seen in the urinalysis report. In the same vein, any dosage beyond prescriber's therapeutic dose as commonly seen among sex workers, and by extension as used by overzealous women of reproductive age group to be abortifacient should be avoided. Significant hypocalcaemia observed in this study was also consistent with increasing strength of Depo-Provera, this could be a window in young women for early precipitation of osteoporosis and its sequelae such as multiple bone fractures perhaps due to loss of bone mineral density (15-17). This is in tandem with the work of Berenson et al. in 2001 which also reflected decrease in serum calcium when Depo-Provera was administered for long period (18). In this regard it will be of benefit if prescribers can add in overzealous administration calcium or vitamin D supplements. Assessment of the urine analysis results showed glomerular leakage of some protein molecules (proteinuria) with a pH of 5.5 in the control and low dose groups, while the moderate and high dose groups reflected moderate bilirubinuria (2+), and severe proteinuria (3+) with a pH of 4.0. As part of its side effects, the increase in bilirubin level has been reported to be due to a blockade of bile duct (19-21).

CONCLUSION

It was evident from the study that administration of low dose Depo-Provera was relatively compatible with the body electrolyte homeostasis but urea and creatinine should be periodically assayed to avert consequential effect that can precipitate renal dysfunction due to accumulation of blood urea and creatinine, and loss of

Table 1: Effect of Medroxyprogesterone on Electrolytes, Urea and Creatinine

Parameter	Control	Low dose (2.14mg/kg)	Moderate dose (4.28mg/kg)	High dose (8.56mg/kg)
Sodium (mmol/L)	158.20±0.82	157.80±0.95	154.32±0.95	128.80±0.45 *
Potassium (mEq/L)	8.15±0.66	7.95±0.75	10.85±0.75 *	11.98±0.17 *
Calcium (mg/dL)	2.60±0.11	2.43±0.10	1.45±0.75 *	1.05±0.04 *
Phosphate (mg/dL)	2.98±0.21	3.01±0.31	3.15±0.19	2.99±1.16
Chloride (mEq /L)	104.20±8.03	96.25±2.92	101.02±4.03	105.03±0.89
Urea (mg/dL)	18.35±2.90	19.08±2.90	26.08±0.90 *	34.53±1.70 *
Creatinine (mg/dL)	36.00±9.73	43.60±2.19 *	44.90±2.19 *	47.20±0.16 *

Level of statistical significance was considered at $p < 0.05$

bone mineral density which may predispose to osteoporosis.

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