THE EFFECT OF CONTRACEPTIVE ADMINISTRATION ON LIPID AND CARBOHYDRATE METABOLISM IN RAT

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ABSTRACT

This study deals with administration of Depo-Provera (injectable contraceptive) to study its effect on lipid and carbohydrate metabolism. The experiment was carried out on 90 adult, mature male albino rats. The animals were divided into:

Group I (Control group).
Group II (low dose treated group).
Group III (high dose treated group).

- Both doses of DMPA exhibited progressive significant ($p < 0.05$) increase in blood glucose level all over the experiment period, (6 weeks) liver glycogen content was increased in both low & high doses treated groups after 6 weeks only, while muscle glycogen content remain on affected during the whole period of the experiment. Serum and liver MDA decreased significantly in both low and high doses treated groups after 4&6 weeks. A progressive significant decrease in kidney MDA was noticed in low and high doses treated groups when compared to control. Neither high dose nor low dose of DMPA causing any significant effect on triglycerides, total cholesterol, HDL, LDL, and total lipids.

INTRODUCTION

In discussions of contraception, the term method effectiveness and use effectiveness are frequently used. Method effectiveness describes the failure rates observed when the method is used correctly 100% of the time and it estimated by lowest observed failure rates (pregnancy).
Use effectiveness is a more practical measure and reflects actual usage, which is often not correct 100% of the time and its estimated by typical user failure rates ***(Schwallie and Assenzo, 1973).***

In 1987, the most frequent used method of contraception is sterilization followed closely by oral contraceptive pills ***(Dilys and Walker, 1993)*** which have been more extensively studied than any other medication and remain the most eff-

ective reversible method of preventing pregnancy ***(Edward and Frederick, 1990).*** Most of these oral contraceptives are combined pills; that consist of various combinations and types of estrogen and progestin**.**

Another means of providing contraception is to inject hormones intramuscularly (I.M.) to create a depot from which the contraceptive agent is gradually released ***(Dilys and Walker, 1993).***

Progestogens have received renewed interest of late because of the reported increased risk of some preparations used in hormone replacement therapy (HRT) ***(Raymond, 2004).***

There are two IPCs (Injectable progestin only contraceptives) that have been available in many countries in the world. These are depot-medroxy-progesterone acetate (DMPA) (Depo-Provera) and norethisterone oenanthate (NET-EN). These are highly effective contraceptives that receive wide acceptance amongst women in their fertile years ***(Draper et al., 2006).***

DMPA has become a popular method of birth control among the adolescent population ***(Cromer et al., 1998),*** and it's a synthetic 17-hydroxymedroxyprogesterone derivative with potential activity, providing long-acting contraceptive protection for 3 months. It's highly effective contraceptive agent and 12-month pregnancy rate are generally lower than oral contraceptives ***(Sapire, 1990 and Ishida et-al; 2002).***

The most important reason to investigate more about Depo-Provera is due to its uses by about 16 million women throughout the world ***(d'Arcangues, 2000).***

The aim of the present study is to investigate the effect of short and long term use of DMPA on carbohydrate and lipid metabolism.

MATERIAL &METHODS

The present study was carried out on a total number of 90 adult, male mature albino rats, weighing 120-180 gm. They were kept for 2 weeks for accommodation and housed in cages under controlled environmental conditions. They were maintained on a standard nutritional formula.

Medroxyprogesterone acetate (MPA) was used in form of Depo-Provera vials (Pharmacia & Upjohn Co.) which is sterile aqueous suspension (1ml) injected deeply I.M. Rats were divided randomly into 3 groups, 30 rats for each group according to duration of the drug administration and dose differences into:-

Group I (control group): 30 rats were injected I.M. with injectable water daily for successive 7 days (10 rats), and for successive 4 and 6 weeks (10 rats for each).

Group II (low dose treated group): 30 rats were injected I.M. with 50 mg DMPA / kg body weight daily for successive 7 days (10 rats), and for successive 4 and 6 weeks (10 rats for each).

Group III (high dose treated group): 30 rats were injected I.M. with 100 mg DMPA / kg body weight daily for successive 7 days (10 rats), and for successive 4 and 6 weeks (10 rats for each).

Blood samples were collected and left to separate clean serum samples for determination of the biochemical parameters such as: blood glucose (BG) ***(Trinder, 1969)***, serum malondialdhyde (MDA) ***(Yoshiko et al., 1979)***, and lipid profile which includes: serum triacylglycerol (TG) ***(Fossati and Prencipe, 1982)***, total lipids ***(Zollner and Kirsch, 1962),*** total cholesterol (TC) ***(Richmond, 1973)***, high density lipoprotein-cholesterol (HDL-Cholesterol) ***(Burstein, 1970 and Lopez-Virella, 1977)*** and low density lipoprotein-cholesterol (LDL-Cholesterol) ***(Friedewald et al., 1972).***

Tissues specimen from liver, kidney, testis and muscle were dissected and separated after decapitation of the rats. Liver, muscle, and kidney washed with normal saline and kept at -20ºC till use for determination of liver glycogen ***(Joltann and Lentini, 1971)***, liver malondialdhyde ***(Yoshiko et al., 1979)***, muscle glycogen ***(Joltann and Lentini, 1971)***, kidney malondialdhyde ***(Yoshiko et al., 1979).***

All data were subjected to statistical analysis according to ***Snedector and Cochran, (1982)*** using a computer program **(Minitab)** by using analysis of variance (F-test) (ANOVA), and then compared by the least significant difference test (LSD-test) at 0.05 level of probability.

RESULTS & DISCUSSION

Table (1) shows the effect of DMPA on blood glucose level (mg/dl), liver glycogen content (µg /mg tissue) and muscle glycogen content (µg /mg tissue) in rat treated groups. It's noticed that along the experimental period was blood glucose level increased significantly in both low & high doses treated groups when compared to control group.

Concerning the dose effect, it's observed that the low dose of DMPA cause a significant increase in blood glucose level after 4&6 weeks. The high dose of DMPA induces progressive significant hyperglycemic along the experimental period. The hyperglycemic effect of DMPA may be due to the glucocorticoid like property ***(Ishida et al., 2000)*** and increased level of growth hormone which antagonize the insulin effect.

On another study ***(Stengard, 1985),*** increased glucose level attributed to high G_{6pase} and low 6PGDH. Decreasing liver G_{6pase} activity and glycogen reserve may be factors contributing the hyperglycemic effect of DMPA ***(Gutheric and John, 1980).***

Increased glucose level may be due to increased intestinal uptake of nutrients as glucose and amino acids by el-evation in sodium dependent glucose uptake and the kinetic parameters of glucose uptake indicate that MPA may induce transporter carrier protein of glucose ***(Nagpaul et al., 1984).***

d'Arcangues (2000) explained the increased level of glucose to increased insulin to glucose ratio suggesting mild insulin resistance. On the same trend, ***Kamau et al., (1990)*** previously recorded that DMPA like other glucocorticoid hormones alters carbohydrate metabolism but development or subject of diabetes hasn't been reported. Diabetes has been rare and no more common than expected among women receiving very large doses of MPA.

Table (1) shows also that both low and high doses treated groups did not inducing any significant differences in liver glycogen content all over the experimental period except after 6 weeks when compared to control group. Neither doses of DMPA (high& low doses) nor duration of the drug administration affect muscle glycogen content along the whole experimental period. These results were supported by the study of ***(Ferrannini et al., 1990)*** who reported that hepatic glycogen synthase was higher than normal in hyperglycemic state, beside enhanced gluconeogenesis. Also blood glucose concentration is the major short term regulator of glycogen synthase activity in liver ***(Kruszynska et al., 1986)***. So, hyperglycemia resulted in increased glycogen content in liver tissue without changes in muscle glycogen content. It's well documented that: MPA exerts some glucocorticoids like activity ***(Gutheric and John, 1980; Kotula et al., 1983).*** However, surprisingly little is known about its effect on liver and muscle glycogen. There are some studies which indicate that MPA treatment may decrease liver G_{6pase} activity and glycogen reserve ***(Gutheric and John, 1980 and Stengard et al., 1984)*** although both of them remain also unaltered except for liver glycogen content after 6weeks in both low and high doses treated groups.

Table (2) shows the effect of DMPA on serum, liver and kidney MDA (Mmol/L). Serum and liver MDA decreased significantly in both low and high doses treated groups after 4&6 weeks. A significant dec-

rease was prominent in high dose treated group when compared to both control and low dose treated groups. A progressive significant decrease in kidney MDA was noticed in both low and high doses treated groups when compared to control (along the course of the experiment).

Findings of ***Tranquili et al., (1995), Pagnini et al., (2000) and Crispino et al., (2004)*** recorded that MPA is a chemosensitizer agent which decreases lipid peroxidation consequently MDA level. The decreased serum MDA level resulted from high dose of MPA may be due to stimulation of superoxide dismutase (SOD.) and catalase which acts as natural biological antioxidant. This suggestion may be coincide with the recent study of ***Crispino et al., (2004)*** who demonstrate that high dose of MPA provide protection from cancer related anorexia / cachexia syndrome (CACs) by modulating cytokines and serotonin production and that such effect is related to oxidative stress.

Table (3) shows the effect of DMPA on lipid profile. Neither doses of DMPA nor duration of DMPA administration causing any significant effect on triglycerides, total cholesterol, HDL, LDL, and total lipids. The administration of DMPA keeping the parameters of lipid profile close to basal level.

Our results concerning lipid profile are in parallel with the findings reported by ***Amatayakul et al., (1980)*** who found that MPA has a minor effect on most lipid parameters. ***Vohra et al., (1985)*** noticed that MPA didn't cause any alterations in cholesterol. ***Main et al., (1995)*** reported that there's no statistical difference in cholesterol, triglycerides,HDL-Cholesterol, LDL. ***Fadden et al., (2004)*** who's reported that DMPA is a safe contraceptive medication by which there is no significant change in both total cholesterol and triglycerides by the injection of DMPA.

Also ***Kaunitz et-al; (2006)*** recorded unchangeable level of triglycerides.

This study suggest that depoprovera is a highly effective, safe and relatively acceptable method of contraception among experimental animals. Careful patient selection with prior counseling and supportive follow up care can significantly support its administration. DMPA is a better choice for progestogen therapy to achieve more beneficial effects on carbohydrate and lipid metabolism.

Table (1): Effect of DMPA on carbohydrate metabolism in treated rats.

	Blood glucose			Liver glycogen			Muscle glycogen		
	1wk.	4wks.	6wks.	1wk.	4wks.	6wks.	1wk.	4wks.	6wks.
Control group	Aa 86.5 ±0.6	Aa 88.5 ±0.6	Aa 88.8 ±0.6	10.06 ±0.04	10.1 ±0.1	Aa 10.2 ±0.1	1.58 ±0.05	1.69 ±0.14	1.76 ±0.08
Low dose	Ab 92.6 ±0.3	Bb 96.5 ±0.4	Bb 96.8 ±0.6	10.0 ±0.2	10.2 ±0.1	Ab 10.3 ±0.1	1.67 ±0.1	1.7 ±0.08	1.88 ±0.05
High dose	Ac 115.6 ±0.6	Bc 123.7 ±0.4	Cc 130.6 ±0.5	10.0 ±0.2	10.2 ±0.1	Bb 11.3 ±0.2	1.78 ±0.06	1.81 ±0.06	1.89 ±0.09

Table (2): Effect of DMPA on MDA in treated rats.

	Serum MDA			Liver MDA			Kidney MDA		
	1wk.	4wks.	6wks.	1wk.	4wks.	6wks.	1wk.	4wks.	6wks.
Control group	0.34 ±0.02	Aa 0.34 ±0.01	Aa 0.33 ±0.03	Aa 0.7 ±0.004	Aa 0.7 ±0.003	Aa 0.69 ±0.001	Aa 0.61 ±0.0001	Aa 0.61 ±0.002	Aa 0.61 ±0.003
Low dose	0.3 ±0.01	Bb 0.27 ±0.01	Cb 0.22 ±0.003	Ab 0.6 ±0.001	Bb 0.59 ±0.002	Cb 0.57 ±0.001	Ab 0.58 ±0.001	Bb 0.55 ±0.001	Cb 0.54 ±0.001
High dose	0.29 ±0.01	Bc 0.22 ±0.01	Cc 0.17 ±0.002	Ab 0.6 ±0.004	Bc 0.57 ±0.002	Cc 0.55 ±0.002	Ac 0.55 ±0.01	Bc 0.52 ±0.01	Cc 0.48 ±0.01

Values represent M.$^{-}$ ± S.E. Values having different small letters in the same column are significantly different at ($p \leq 0.05$), while values having different capital letters in the same raw are significantly different at ($p \leq 0.05$).

Table(3) :Effect of DMPA on lipid profile in treated rats.

Duration	T.G.			T.C.			HDL			LDL			T.L.		
Groups	1 Wk.	4 Wks.	6 Wks.	1 Wk.	4 Wks.	6 Wks.	1 Wk.	4 Wks.	6 Wks.	1 Wk.	4 Wks.	6 Wks.	1 Wk.	4 Wks.	6 Wks.
Control Group	95.07 ±0.4	95.8 ±0.47	96.79 ±0.48	97.37 ±0.41	97.65 ±0.51	97.82 ±0.4	23.7 ±0.3	23.45 ±0.3	23.34 ±0.25	54.9 ±0.3	55.0 ±0.5	55.9 ±0.6	346.91 ±0.87	345.62 ±1.22	345.16 ± 2.13
Low Dose	95.34 ±0.56	95.93 ±0.74	97.15 ±0.47	97.65 ±0.46	97.96 ±0.4	98.2 ±0.2	23.4 ±0.6	22.33 ±0.52	22.2 ±0.5	55.7 ±0.7	56.3 ±0.5	57.9 ±0.8	346.53 ±1.0	345.23 ±0.37	344.2 ±0.49
High dose	96.45 ±0.67	96.93 ±0.66	97.73 ±0.51	97.8 ±1.2	98.3 ±0.5	98.7 ±0.3	22.67 ±0.99	22.27 ±0.3	22.13 ±0.2	56.9 ±0.7	56.9 ±0.5	58.1 ±0.8	345.45 ±0.7	344.01 ±0.62	343.07 ±0.3

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الملخص العربى

تأثير تعاطى موانع الحمل على التمثيل الغذائى للدهون و الكربوهيدرات فى الفئران

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تهدف هذة الدراسة الى تقييم تاثير تعاطى أحد موانع الحمل (ديبو- بروفيرا) على التمثيل الغذائي للدهون والكربوهيدرات في الفئران.

أجريت الدراسة علي ٩٠ فأر ذكر أبيض وقسمت الحيوانات الى ثلاث مجموعات كالتالي:

أ- المجموعة الضابطة.

ب- المجموعة المعاملة بالجرعة المنخفضة.

ج - المجموعة المعاملة بالجرعة العاليه.

تم تجميع عينات الدم وتترك لتتجلط ثم فصل المصل ، وتم تقدير القياسات التالية: قياس معدل الجلوكوز في المصل و تقدير محتوى الجليكوجين في انسجة الكبد والعضلات ، قياس محتوى الاكسدة فوق الدهنية في المصل وفي أنسجة الكبد والكلى وقياس الدهون الكاملة متمثلة في محتوى الجليسريدات الثلاثية والكوليستيرول والكوليستيرول عالي ومنخفض الكثافة والدهون الكلية.

تتلخص نتائج الدراسة في التالي:-

١- أظهرت المجموعات التى حقنت بالجرعه المنخفضة زيادة في معدل الجلوكوز في الدم عند مقارنتها بالمجموعة الضابطة على مدارفترة التجربة.بينما أحدثت الجرعة العالية زيادة معنوية متدرجة في مستوى الجلوكوز علي مدار فترة التجربة في الدم عند مقارنتها بالجرعة الأقل وبالمجموعة الضابطة.

٢- لم يتأثر محتوى الجليكوجين في الكبد الا بعد الاسبوع السادس فى كلا من المجموعة التى عوملت بالجرعة العالية والمنخفضه فى حين أن محتوى الجليكوجين فى العضلات لم يتأثر معنويا باستخدام الديبو بروفيرا على مدار التجربة.

٣- نقص معنوي فى محتوي الاكسدة فوق الدهنية فى المصل والكبد بعد الاسبوع الرابع والسادس في المجموعات المعاملة بالجرعتين العالية والمنخفضة من الدواء. أما محتوي الاكسدة فوق الدهنية في الكلي فقد حدث به نقصاً معنوياً مستمراً علي مدار التجربة فى كل المجموعات. وأظهرت المجموعة المحقونه بالجرعة العالية نقصا أكثر معنوية فى محتوي الاكسدة الفوقيه للدهون في الكلي عن المجموعات التى عوملت بالجرعه المنخفضه والمجموعه الضابطه.

٤- لم يتسبب الدواء في احداث أي تأثير معنوي في معدلات الدهون الكاملة في المصل والتى تشمل محتوى الجليسريدات الثلاثية والكوليستيرول والكوليستيرول عالي ومنخفض الكثافة والدهون الكلية سواء مع استخدام الجرعات العالية أو المنخفضة من الديبوبروفيرا علي مدار التجربة.
وقد نوقشت نتائج الدراسة مع نتائج الابحاث السابقة.

نستخلص أن عقار الديبوبروفيرا وسيله مؤثره وامنه ومقبوله لمنع الحمل في السيدات.
ونوصى أن نأخذ الاحتياطات المقصوده عند استعمال الديبوبروفيرا مع مرضى السكر من السيدات.