COMPARATIVE STUDY OF ALKYLATING AND NON-ALKYLATING ANABOLIC STEROIDS: EFFECTS ON LIVER, REPRODUCTIVE AND IMMUNE SYSTEMS ON ADULT ALBINO RATS

Thesis submitted in partial fulfillment for the MD degree
In Forensic Medicine and Clinical Toxicology
By

Iman Mohamed Fawzy Gaballah
Assistant Lecturer of Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Cairo University

Under the supervision of

Prof. Dr. Aly Gamal-El-din Abdel-Aal
Professor and Head of Forensic Medicine and Toxicology Department,
Faculty of Medicine, Cairo University

Prof. Dr. Abla Abd-El-Meguid Attia
Professor of Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Cairo University

Ass.Prof. Amany Salah Mohamed
Assistant Professor of Forensic Medicine and Clinical Toxicology,
Faculty of Medicine, Cairo University

Ass.Prof. Manal-El-Sayed El-Halwagy
Assistant Professor of Biochemistry, Mammalian Toxicology Department,
Central Pesticide Laboratory

2009

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ABBREVIATIONS

1.	17α-aas	: 17 α-alkylated steroids.
2.	AAS	: Androgenic Anabolic Steroids.
3.	Ab	: Antibody.
4.	ABC	: ATP Binding Cassette.
5.	Ag	: Antigen.
6.	ALT	: Alanine Aminotransferase.
7.	AR	: Androgen Receptor.
8.	AST	: Aspartate Aminotransferase.
9.	BSEP	: Bile Salt Export Pump.
10.	CD	: Cluster of Differentiation.
11.	CH3	: Methyl Group.
12.	CK	: Creatine Kinase.
13.	CYP	: Cytochrome P450.
14.	DHT	: Dihydrotestosterone.
15.	FSH	: Follicle Stimulating Hormone.
16.	GGT	: Glutamyl Transpeptidase.
17.	GSH	: Reduced Glutathione Levels.
18.	H&E	: Haematoxylin & Eosin.
19.	HDL.	: High Density Lipoproteins
20.	HREs	: Human Response Elements.
21.	Ig	: Immunoglobulins.
22.	IL	: Interleukins.
23.	LDL	: Low Density Lipoproteins.
24.	LFT	: Liver Function Tests.
25.	LH	: Leutinizing Hormone.
26.	METS	: Mitochondrial Electron Transport System.
27.	NK	: Natural Killer.
27.	ROS	: Reactive Oxygen Species.
27.	SHBG	: Sex Hormone Binding Globulin.
30.	T	: Free Testosterone.
31.	T1/2	: Half Life.
32.	TRT	: Testosterone Replacement Therapy.

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ACKNOWLEDGEMENT

I would like to express my gratitude and sincere thanks to **Prof. Dr. Aly Gamal El-Din**, Professor of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Cairo University, and the senior supervisor for his unfailing scientific support, sincere encouragement, and valuable guidance.

My deepest thanks should go to **Prof. Dr. Dina Ali Shokry**, Professor and Head of the Forensic Medicine and Clinical Toxicology Department for her cordial love and support.

I would also like to express my sincere gratitude and deep appreciation to **Prof. Dr. Abla Abdel-Meguid Attia**, Professor of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Cairo University, for suggesting the idea and plan of the work, for her faithful guidance and continuous efforts to ease the difficulties encountered during this work.

I offer my great appreciation and thanks to **Dr. Amany Salah**, Assistant Professor of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Cairo University for her meticulous supervision, sincere guidance and kind help in every step of the work.

I also offer my deepest thanks and gratitude to **Dr. Manal El-Halwagy**, Assistant Professor of Biochemistry, Mammalian Toxicology Department and Central Pesticide Laboratory for her continuous help, meticulous supervision and continuous encouragement.

Thanks should also go to **Prof. Dr. Nevein Darwish**, Professor of Pathology, Research Institute of Ophthalmology, for her artistic and scientific role in processing and reading the histopathological part of this work.

ABSTRACT AND KEYWORDS

ABSTRACT

Androgenic anabolic steroids (AAS) are widely used by athletes, bodybuilders and adolescents for performance enhancement. They are either consumed orally or by injection. More than 100 different AAS are used illegally. The aim of the present study was to compare alkylating and non-alkylating AAS effects on the liver, immune system and reproductive system. Anabol, nandrolone and both drugs stacked were used in therapeutic, low toxic and high toxic doses. 374 adult male albino rats (~100-120gms) were divided into 3 groups (128 each) according to drug used, and then subdivided into 3 subgroups (32 each) according to dose. Drugs were given for 3 months then discontinued for an extra month to allow for recovery. At the end of each month, the rats were weighed, blood samples collected and tissues obtained for histopathological examination. The results of the present study revealed affected liver functions in the form of increased AST, ALT, total proteins, albumin and GSH, while MDA showed no change. It should be noted that oral steroids showed maximum effects. However, IgG and IgM revealed maximum elevation with the oral and maximum depression with the injectable AAS. Testosterone hormone decreased maximally in the stack-treated rats. Affection was maximum in G3 of the 3rd period. Recovery occurred in the 4th period but normalization was incomplete. Histopathology confirmed these changes.

KEYWORDS

Anabolic androgenic steroids (AAS), hepatotoxicity, immunotoxicity, antioxidants and reproductive systems.

Introduction & Aim of the work

INTRODUCTION

Anabolic androgenic steroids (AAS) are either endogenous occurring naturally within the body (e.g. testosterone, androstenediol, dihydroepiandrosterone) or exogenous synthetic derivatives of testosterone (e.g. anabol and nandrolone decanoate) **(Socas et al., 2005)**.

Testosterone is a C_{19} steroid hormone that exists both free and bound to plasma proteins. It is the natural male hormone which is produced primarily by the testis. It is also produced by females but in lesser amounts. It is responsible for the androgenic (masculinizing) and anabolic (tissue building) effects throughout male adolescence and adulthood **(Moretti et al., 2007)**.

Anabolic steroids are synthetic derivatives of testosterone. They are divided into two main groups: those with alkylation of 17-α position with ethyl or methyl group and those with esterification of 17-β-OH group. These modifications enable these chemical compounds to have prolonged physiological effects up to several months **(Karbalay-Doust et al., 2007)**.

Anabolic steroids are usually administered orally as well as by injection. They are used by athletes to enhance performance and by non-athletes to enhance appearance. Although their use is illegal and banned by virtually every sport-governing body, yet, survey and drug-testing data indicate continued use by competitive athletes at all levels. The fact that the frequency of steroid use appears to have increased significantly over the past three decades among adolescents, women and recreational athletes is of growing concern. Their abuse presents an interesting

public health challenge, as they are associated with deleterious physical and psychological outcomes **(Di Luigi et al., 2005; Aede de Groot and Willem, 2006)**.

Strong evidence exists demonstrating that AAS result in increased body weight and muscular strength. However, there is also increasing evidence that their abuse is associated with adverse effects on the liver, serum lipids and the reproductive system. These effects are also associated with increased levels of irritability, aggression, personality disturbance, dependence and psychiatric ailments **(Estrada et al., 2006; Samaha et al., 2008)**.

Aim of Work:

This work aimed at comparing the effects of alkylating and non-alkylating AAS on the liver, the immune and the reproductive systems of adult male albino rats using therapeutic, low toxic and high toxic doses.

Chapter One

NATURALLY OCCURRING STEROIDS

PRODUCTION OF NATURAL STEROIDS

Testosterone (4-androstene-3-ol, 17β-ol) is a natural steroid hormone belonging to the androgen group. It is primarily secreted in the testes of males and the ovaries of females. Small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. Large amounts are produced by Leydig cells of the testis but smaller quantities are also produced in women by thecal cells of the ovary, by the placenta, as well as by the zona reticularis of the adrenal cortex in both sexes. The male generative glands contain Sertoli cells which require testosterone for spermatogenesis. Testosterone is supplied to target tissues in the blood where most of it is transported bound to specific plasma protein called Sex Hormone Binding Globulin (SHBG) **(Hulmi et al., 2008)**.

BIOCHEMISTRY OF TESTOSTERONE

Testosterone is identified chemically as 17β-OH androst-4-ene-3-one ($C_{19}H_{28}O_2$), a solid polycyclic alcohol with an -OH at C_{17} (Fig. 1). Sometimes other side chains can be added. These are known as esters and are formed of C, H and O. These control the rate by which the steroid is released into the blood stream. Large esters are released slowly because they decrease the solubility of the steroid in water and increase its fat solubility **(Aede de Groot and Willem, 2006).**

When a steroid has an ester attached, it is rendered inactive because the ester prevents it from binding to a receptor. In order to become active again, the enzyme esterase must detach the ester and restore the hydrogen to form the -OH group attached to C_{17}. Esters are usually

attached at C_{17}, though they are sometimes found at C_3. Testosterone is easily converted in the body into Dihydrotestosterone (DHT) by the enzyme 5α reductase. Some steroids undergo conversion of androgen into estrogen which is catalyzed by the enzyme aromatase by a process known as aromatization. When Testosterone is aromatized, it is converted into estradiol (Fig. 2) **(Aede de Groot and Willem, 2006)**.

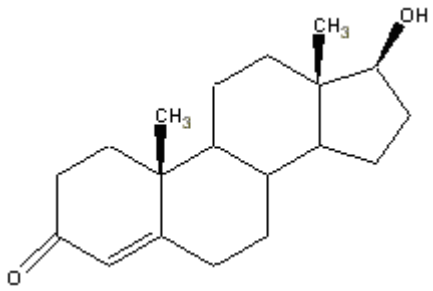

Fig. 1: Chemical Structure of Testosterone **(Aede de Groot and Willem, 2006).**

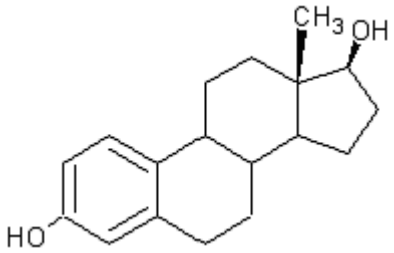

Fig. 2: Chemical Structure of Estradiol **(Aede de Groot and Willem, 2006).**

In men, testosterone plays an important role in health and well-being. An adult human male produces about 40-60 times more testosterone than an adult female, but females, from a behavioral perspective (rather than from an anatomical or biological one), are more sensitive to the hormone **(Pike et al., 2006).**

PHYSIOLOGICAL EFFECTS OF TESTOSTERONE

- **Anabolic Effects:** These are directed towards growth of muscle mass and strength, increase in bone density and strength, stimulation of linear growth and bone maturation **(Moffat et al., 2005)**.
- **Androgenic Effects:** These are responsible for maturation of external genital organs particularly in unborn children. At puberty, secondary sex characters appear as for instance, deepening of voice, growth of beard and appearance of axillary hair **(Moffat et al., 2005)**.