HISTOMORPHOLOGICAL STUDIES OF THE EFFECTS OF AMODIAQUINE ON THE OVARY IN SPRAGUE-DAWLEY RATS

BY

GBOTOLORUN, Stella Chinwe

Matric No. 209091005

SEPTEMBER, 2010

HISTOMORPHOLOGICAL STUDIES OF THE EFFECTS OF AMODIAQUINE ON THE OVARY IN SPRAGUE-DAWLEY RATS

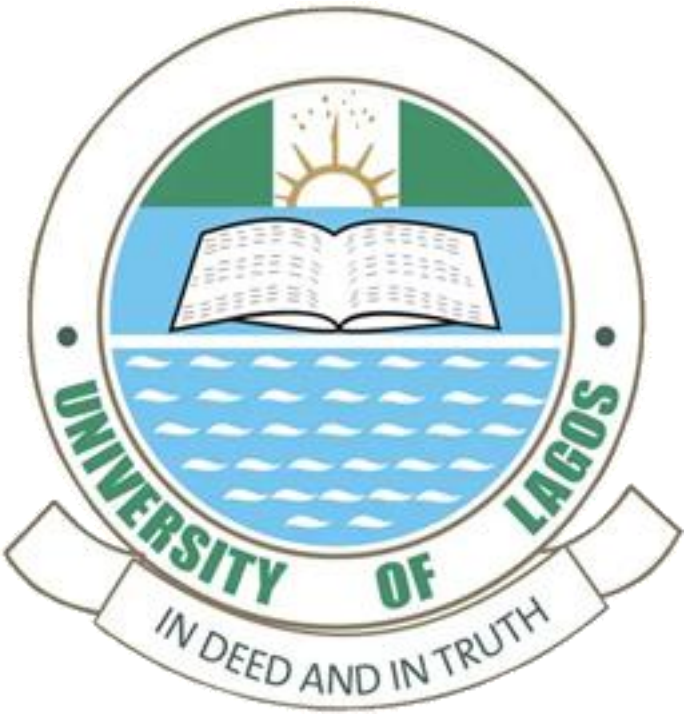
THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES, UNIVERSITY OF LAGOS, IN FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.) IN THE DEPARTMENT OF ANATOMY, COLLEGE OF MEDICINE OF THE UNIVERSITY OF LAGOS, LAGOS, NIGERIA

BY

GBOTOLORUN, STELLA CHINWE

B.Sc. Anatomy (Portharcourt, 1998), M.Sc. Anatomy (Lagos, 2002)

SEPTEMBER, 2010


UNIVERSITY OF LAGOS
IN DEED AND IN TRUTH

DECLARATION

We hereby declare that the thesis titled "HISTOMORPHOLOGICAL STUDIES OF THE EFFECTS OF AMODIAQUINE ON THE OVARY IN SPRAGUE-DAWLEY RATS" is a record of original research work carried out by GBOTOLORUN, Stella Chinwe in the Department of Anatomy, College of Medicine of the University Of Lagos, Nigeria.

S.C GBOTOLORUN
CANDIDATE …… ……...
SIGNATURE DATE

DR. A.A.A. OSINUBI
(SNR LECTURER)
SUPERVISOR …… ……
SIGNATURE DATE

DR. C.C. NORONHA
(SNR LECTURER)
SUPERVISOR …… ……..
SIGNATURE DATE

DR. A.A. OREMOSU
(SNR LECTURER)
SUPERVISOR …… ……..
SIGNATURE DATE

DEDICATION

This work is dedicated to my darling husband Olalekan, and my lovely children, Ayooluwa and Anuoluwapo who have made my life more meaningful and purposeful. God bless you all.

ACKNOWLEDGEMENTS

What will it profit a man if he gains the whole world and loses his soul? That is the biggest question everyone must ask himself/herself one day and I want to thank God Almighty that he has helped me answer this question truthfully and also to make the right choice. I want to also thank God for life and inspiration because "in Him I live and move and have my being".

My sincere appreciation goes to Professor A.O. Okanlawon, Proffessor of Anatomy for his support and encouragement during the period of this study. To my supervisors, I say God bless you; Dr. C.C. Noronha, mom, words are not enough to express my appreciation for your motherly love, support and mentorship; Dr. A.A.A. Osinubi, "Egbon" you have been a great source of inspiration and encouragement to me; and Dr A.A. Oremosu, you have been a teacher and a friend- thank you.

I also wish to express my sincere appreciation to Drs Duru, Ibeabuchi and Olabiyi for their judgemental and critical contributions towards this study. To my other colleagues, Drs Aiyegbusi, Kusemiju and Yama, Mrs Dosumu, Ini-Okoko, Bakare, I say thank you.

I also wish to acknowledge Professor H.A.B. Coker, Dean, Faculty of Pharmacy for his immense contributions towards this study: he helped to programme and channel my thoughts and also for the pure substance of amodiaquine used for this study. Dr Silva of the Faculty of Pharmacy I say thank you for your encouraging words all the time and for your contributions.

I express my sincere appreciation to Professor Banjo and Dr Anunobi of the department of Morbid Anatomy. To my parents Mr J.C Ndife and Mr and Mrs Gbotolorun, thank you for your support and encouragement. To my Daddy, i say thank you for believing in me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF PLATES

ABSTRACT

The prevalence of female infertility ranges from 7 to 28% depending on the age of the woman. Although the origin and frequency of infertility vary about 40 to 50% of the aetiology of infertility cases is as a result of female factors. Malaria and the treatment of malaria have being a major challenge for decades. A number of antimalarial drugs have been reported to have anti-fertility actions.

Amodiaquine (AQ) is an anti-malarial drug and belongs to a class of drugs known as the 4-aminoquinolines. It was removed from the essential drug list in 1990 as a result of hepatoxicity and agranulocytosis that occurred with long- term use. AQ is now making a comeback and is in the spotlight as a partner drug with artemisinins in the World Health Organization (WHO) recommended artemisinin based combination therapies (ACTs). In malaria-endemic regions of the world, self medication with antimalarial drugs is common and it is possible for a person to be treated several times in a year. With the frequency of treatment the risk of adverse events associated with long-term use of AQ may arise.

A number of investigators have carried out studies on the effect of AQ on pregnancy and pregnancy outcomes, however, there remains a dearth of literature on the short-term or long-term effect of AQ on the structure and function of the ovary in the non-pregnant female.

This study was carried out to investigate the histomorphological changes and responses of the ovary of Sprague-Dawley rats to AQ administration. The study was divided into 4 experimental groups. AQ was given at a dose of 6.0 and 12 mg/kg bw via oral and intraperitoneal routes for 28 days. Vitamin C was administered at a dose of 0.1 mg/kg bw 3 days in a week while Vitamin E was given at a dose of 20 mg/kg bw 5 days in a week. In each of the experiments AQ was administered alone, co-administered with

Vitamin C and co-administered with Vitamin E (AQ alone, AQ + Vitamin C and AQ + Vitamin E) according to the treatment protocol. At the end of the experiment all the animals were sacrificed by cervical dislocation.

Oestrus cycle was determined using the vaginal smear method and ovulation was determined at 10:00hr on the day of estrus. The ovary was dissected and processed for histology, assayed for superoxide dismutase and catalase activities and also assayed for reproductive hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL).

The result of the oestrous cycle showed that AQ prolonged the length of the oestrous cycle and was statistically significant in the group that received 12 mg/kg bw via intraperitoneal route. Co –administration of AQ + Vitamin C increased the cycle length even further and was statistically significant ($p < 0.05$) except in the group that received 6 mg/kg bw intraperitoneal route. The ovulation studies showed that AQ reduced the number of ova that was shed in the morning of estrus and was statistically significant ($p < 0.05$) in the group that received 6.o and 12 mg/kg bw oral route.

Histology of the ovary showed that AQ increased the number of atretic follicles when compared with the control. There appeared to be more atretic follicles at 12 mg/kg bw than at 6.0 mg/kg bw AQ. AQ caused reduction in the activities of superoxide dismutase and catalase in the ovary and was statistically significant ($p < 0.05$) in the groups that received AQ + Vitamin C.

The expected surge in FSH, LH and PRL between 5 to 7 p.m. on proestrus that is expected for the follicular rupture that occurs at ovulation was experienced in this study. There was no statistically significant difference in the serum concentration of these hormones when compared with the control group. The results obtained in this study shows that AQ is deleterious to the ovary.