FORMULATION OF QUININE SUPPOSITORY AND EVALUATION OF QUININE UPTAKE IN THE MOUSE BRAIN

BY

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NOVEMBER 2010

FORMULATION OF QUININE SUPPOSITORY AND EVALUATION OF QUININE UPTAKE IN THE MOUSE BRAIN

A THESIS SUBMITTED TO THE UNIVERSITY OF LAGOS, NIGERIA

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF DOCTOR OF PHILOSOPHY (Ph.D.) IN CLINICAL PHARMACY

BY

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NOVEMBER 2010

SCHOOL OF POSTGRADUATE STUDIES
UNIVERSITY OF LAGOS

CERTIFICATION

This is to certify that the Thesis:

"FORMULATION OF QUININE SUPPOSITORY AND EVALUATION OF QUININE UPTAKE IN THE MOUSE BRAIN"

Submitted to the
School of Postgraduate Studies
University of Lagos

For the award of the degree of

DOCTOR OF PHILOSOPHY (Ph.D.)

is a record of original research carried out
By

SOREMEKUN, REBECCA ORITSEMAJE

In the Department of Clinical Pharmacy and Biopharmacy

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DEDICATION

I dedicate this work to my husband, Olukayode Akinyemi Soremekun for his love and unflinching support as regards the progress and development of my career. My daughters: Olumayokun, Yemisi, Eniola, Ayokunmi , Oluwatoowo and Opemipo have a pride of place in my life and by extension in the completion of this work.

ACKNOWLEDGEMENTS

I thank the almighty God for His hands that have been at work in my life. It was Him that put a detour in my career path such that I could not embark on the Ph.D. route until now. He is the mighty artist who has the full picture. I appreciate Him daily even as the picture emerges.

I also wish to place on record my sincere appreciation of my supervisor: Prof Fola Tayo. Professor Tayo's avuncular dispositions are such that his thoroughness and cerebral inputs course through the work. For all these and more, I sincerely appreciate you sir. I also wish to appreciate my second supervisor, Prof Cecilia Igwilo. Her initial and continuous encouragement inspired me to pursue an academic career. My sincere appreciation also goes to Dr Lanre Silva whose tremendous encouragement helped me to struggle on through the tough times. Dr Silva was more like a third supervisor. I must also appreciate the dedication of Mr Ojobo, the technologist at the Central Research laboratory of the College of Medicine. He is an epitome of diligence and I have no doubt that he will attain great heights. I also wish to appreciate the Dean of the Faculty, Prof HAB Coker for his concern and constant advice. Prof Omilabu also deserves mention. He made out time to put me through on the use of the fluorescent microscope and made same available for my use. Mr Seyi Campbell who provided assistance with the light microscopy also deserves my gratitude. I also wish to appreciate the technical staff of the Department of Clinical Pharmacy especially; Mrs Adams, Mrs Abbey and David. They were most supportive in the course of this work. To all my colleagues in the Department, permit me to say that; you make the environment more conducive and interesting. Thank you very much.

Lastly, I appreciate the love and prayers of my biological and spiritual siblings. I pray that my father, the Almighty God will reward you all beyond measure. God bless you all.

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ABSTRACT

The occurrence of resistance to chloroquine and sulfadoxine/pyrimethamine by *Plasmodium falciparum* stimulated new interest in quinine for treating multi-resistant *falciparum* infection. Parenteral quinine is the gold treatment in the management of severe and complicated malaria. There is the need for early initiation of treatment in management of complicated malaria. An antimalarial drug to be used at home must be safe, effective, affordable and easy to administer A rectal formulation of quinine will serve the purpose of home initiation of treatment. The main objective of this work was to develop a stable quinine suppository that will ensure adequate release of quinine and evaluate quinine uptake into the four sections of the mouse brain

Cocoa butter and Fattibase ^{TM} were used in the preparation of suppositories containing 200mg quinine bisulphate. The release profiles of the formulations with varying concentrations of polysorbate 80 (0, 1, 2 and 5%) were evaluated by in-vitro dissolution in pH 8 buffer medium. Evaluation of brain uptake was carried out in various stages using the murine mice model. Quantification of uptake into the four brain sections was done with a High Pressure Liquid Chromatography technique. Uptake was compared in the four brain sections of parasitized and non-parasitized murine mice as a function of time (30, 60, 120, 180, 240 min). Quinine uptake from suppository was also compared with uptake from peritoneal injection in parasitized and non-parasitized. The values obtained were subjected to statistical analysis using the 3-way ANOVA.

The Formulations of suppositories in cocoa butter and Fattibase^{TM} released quinine in adequate quantity. Addition of polysorbate 80 improved release of quinine significantly ($P = 0.005$ for cocoa butter and $P = 0.003$ for Fattibase^{TM}). Cocoa butter with 1% Polysorbate 80 released 36.8% quinine bisulphate in 60 min while release from suppositories with 2% and 5% surfactant was erratic. Fattibase^{TM} suppositories with 5% polysorbate 80 released 85% quinine content in 60min. This formulation was stable in the refrigerator for three months while samples stored at

ambient temperature were stable for one month. From the release profiles, three formulations have very high potentials in management of cerebral malaria: cocoa butter+1%, Fattibase^{TM} + 2% and 5% respectively.

Fluorescence microscopy revealed green fluorescence characteristic of quinine in the brain sections of parasitized and non-parasitized mice treated with quinine. Quinine crossed the blood brain barrier into the brain in parasitized and non-parasitized mice. This confirms that inflammation is not required for the transport of quinine bisulphate into brain. Quinine from the suppository was available in the brain in 30 min. Uptake had a significant time–dependence (P=0.000). Uptake in parasitized mice was significantly higher than that in the non-parasitized mice (0.000). Quinine uptake varied significantly in the four brain sections with olfactory lobe recording the highest uptake in the two groups of mice (0.000). Quinine uptake in the parasitized mice is biphasic while a steady decline was observed in non-parasitized mice over the time period. The concentration of quinine taken up by other brain sections: cerebrum, cerebellum and medulla oblongata was significantly lower than the concentration in the olfactory lobe with cerebrum having the lowest uptake in the parasitized mice.

This intra-rectal formulation will be useful in pre-referral management procedures in primary health facilities, homes and rural areas.