Available online at www.ujpronline.com
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

RESEARCH ARTICLE

COMPARATIVE CURE AND SUPPRESSION EFFICACY OF FORMULATED GRANULES WITH A MARKETED SIMILAR PRODUCT

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Article Info:

Article History:
Received: 17 May 2024
Reviewed: 12 July 2024
Accepted: 20 August 2024
Published: 15 September 2024

Cite this article:
Edwin AU, Emmanuel AU. Comparative Cure and Suppression Efficacy of formulated granules with a marketed similar product. Universal Journal of Pharmaceutical Research 2024; 9(4): 69-71. ***http://doi.org/10.22270/ujpr.v9i4.1164***

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Abstract

Aim and Objectives: Malaria, a major global health challenge which makes antimalarial drugs one of the commonly prescribed class of drugs World-wide. The most vulnerable are the children and the women especially the expectant mothers. There is need to develop locally and readily available excipients from natural sources to replace imported ones currently being used by our local manufacturing industries. The purpose of the investigation was to test the formulated granules for oral suspension.

Methods: Some weighed albino rats were infected with *Plasmodium berghei*, then the standard dose of the artemether-lumefantrine oral suspension formulated, a marketed product, and distilled water were administered ; 4/24 mg artemether-lumefantrine per kg body weight per oral to weighed albino rats. Then, other groups were administered standard dose of different formulated granules, a marketed similar product and distilled water respectively. These treated albino rats were then infected with *Plasmodium berghei* and blood samples were withdrawn from the tail veins, stained with Giemsa stain and the *Plasmodium berghei* count for the untreated and treated albino rats were determined.

Results: The percentage clearance and suppression were calculated for the different formulations; pectin and its hybrid formulations, a marketed product and distilled water as a control which were 83.73, 85.2, 74.9 and 2.62, and 83.74, 85.2, 74.22, and 0% for curative and suppressive efficacies respectively.

Conclusions: The investigations revealed that the most effective was the hybrid-formulated granules were closely followed by pectin-formulated granules and the least was the marketed product.

Keywords: Artemether, characterization, clearance, extracted pectin, hybrids lumefantrine, suppression.

INTRODUCTION

Malaria is an infectious disease caused infected female anopheles mosquitoes; though preventable and curable. There are five parasite species that transmit malaria in humans; *Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax, Plasmodium ovule, Plasmodium knowlesi*, but, two of them pose the greater threat; *P. falciparum* and *P. vivax.* In 2019, almost half of the world's population was at risk of malaria, but most of the cases and death occur in Africa. High malaria infestation was attributed to the level of poverty in the African Continent, hence the need for the increment of dosage forms and assessment of their efficacy. Ascertaining such efficacy reduces treatment failure leading to complete eradication and reduced disease states and death resulting from malaria infestation. Children under five years of age are the most vulnerable, two-third of all malaria deaths World Wide[1]. Malaria spreads when a mosquito becomes infected with the disease after biting an infected person, and the infected mosquito then bites a non-infected person. The malaria parasites enter that person's bloodstream and travel to the liver. When the parasites mature, they leave the liver and infect red blood cells[2].

Vector control is acts of malaria control and elimination strategies and quite effective in preventing infection and reducing disease transmission. The two popular methods being used globally include the use of the insecticide - treated nets (ITNs) and indoor residual spraying (IRS). Malaria control has however being threatened by emerging resistance strains to insecticides among anopheles mosquitoes; 78 countries reported mosquito resistance to at least one of the four commonly used insecticide classes between 2010 and

2019. While 29 countries reported mosquito resistance to all the used insecticide classes[1].

Prevention chemotherapies

This is using of pharmaceuticals/drugs, either singly or in combination to prevent malaria infestation and diseases. These are practiced as; Intermittent Preventive Treatment of Infants (IPT_I) and Intermittent Preventive Treatment of Pregnant Women (IPT_P), Seasonal Malaria Chemoprevention (SMC) and Mass Drug Administration (MDA). These measures are to complement ongoing malaria control activities[1,2].

Malaria vaccine

The first vaccine for malaria has been developed after more than 30 years of work and about $1 billion in investment by Glaxo-Smithkline Plc and its partner won a recommendation from the world Health Organization, WHO today for use in children in Saharan Africa and other regions with moderate to high transmission. This vaccine administration with anti-malarial drugs has reduced malaria cases and death by about 70% among the children population[3].

Symptoms of malaria

Pains in the muscle or abdomen, whole body: fever, chills, fatigue, malaise, shivering or sweating. Gastrointestinal: nausea or vomiting. Also common: headache, fast heart rate, or pale skin[3,4].

Malaria management

Diagnosis and commencement of treatment reduces the disease, prevents death and reduces transmission. All suspected cases of malaria must be confirmed using parasite-based diagnostic testing (through either microscopy or a rapid diagnostic test). This is to enable health care providers distinguish between malarial and non-malarial fevers and facilitating appropriate treatment. Treatment consists of anti-malarial agents; people travelling to areas where malaria is common typically take protective drugs before, during, and after their trip. Treatment includes anti-malarial drugs. Suffice to mention that earlier resistance had been developed to anti-malarial like quinine and chloroquine, so the best available treatment particularly to *P. falciparum* malaria is artemisinin-based combination therapy (ACT) for quick and complete eradication of *plasmodium* parasites from patients' circulatory system[5,6].

Dosage

It is a function of the severity of the case and the clinical manifestation of the patient. However, the standard dose is general 4/24 mg artemether/ lumefantrine per kg body weight respectively per day, administered 12 h (WHO 2021).

MATERIALS AND METHODS

These include, but, not restricted to albino rats, distilled water, 0.5 mL syringe/needle, heparinized tubes, Giemsa stain, *P. berghei* infected albino rats, *P. berghei* obtained from Nnamdi Azikiwe University, Awka. Antimalarial curative study of the optimized formulated and marketed granules for oral suspension was carried out according to animal model study by Peter, 1975 with some modifications. In this model of study, a total of twenty male albino mice of weight 20± 2 g in groups of five mice. Blood was collected from the mouse infected with the parasite, *P. berghei* by oculus puncture and was diluted with 0.9 %w/v sodium chloride that 0.2 mL contains approximately 10^7 infected erythrocytes. All the animals in each group were infected with the parasite by single intra-peritoneal administration of 0.2 mL of the diluted blood and left for 72 h[7]. Then each of the four groups was administered with 0.2 mL of distilled water, D/W, the normal dose 4/24 mg artemether-lumefantrine per kg body weight of the marketed product, N, optimized formulations with the extracted pectin, M and the hybrid, G, respectively for three days. A thin film of blood made from the tail blood stained with a Giemsa stain and was examined for parasitemia on day 4 and 7 respectively. The percentage curative was calculated using the formula;

$$\% \text{ curative} = \frac{D_A - D_B}{D_A} \times 100$$

Where; D_A= Mean parasitemia count of the untreated group, D_B= Mean parasitemia, count of the artemether - lumefantrine treated group

The survived mice had their parastemia levels examined on day 8, 12, 15, and 30 post treatments with much care and observations of signs and behavior.

Ethical approval

Issued on the 8 December, 2023 by the Ethical committee of University of Port Harcourt, Rivers State.

Statistical analysis

Results were expressed as mean ± standard deviation and the differences compared using one-way ANOVA.

RESULTS AND DISCUSSION

The essence of designing a formulation is to enhance its efficacy and/or therapeutic effects. Results from the animal study indicated that the three formulations, optimized formulations M and G, and the marketed product, N administered were efficacious. However, the order of efficacy was N<M<G as shown in Figure 2. The formulation of the marketed product has the least percentage clearance, but the formulation with the hybrid, G had the highest percent clearance. Though, the clearing ability of the hybrid formulation in the plasma similar to that formulated with pectin, but, pectin is more readily available in the country and will definitely be less costly than the hybrid formulation which contains xanthan gum which is not readily/ locally available[8,9].

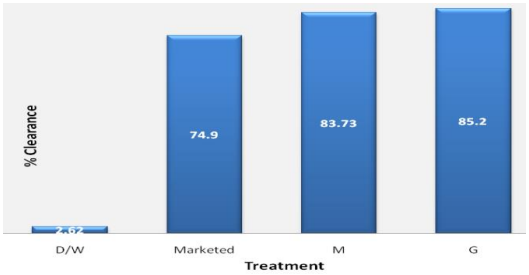

Figure 1: The Curative effect of the formulated artemether-lumefantrine granule and a marketed product on the *P. berghei* parasites.

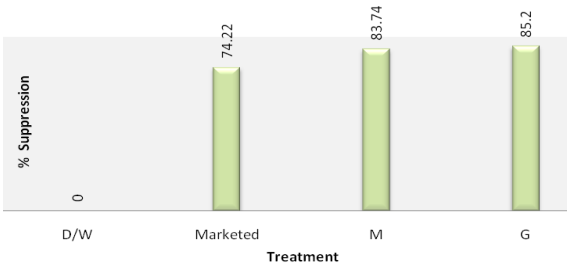

Figure 2: The chemoprophylactic effect of the artemether-lumefantrine formulations and a marketed product on *P. berghei* parasites.

Evaluation of the chemoprophylactic potential of the formulated artemether-lumefantrine fixed- dose therapy was performed according to Peter, W, 1975 with some modifications. Four groups of five mice each group was administered with standard dose of formulated products, (pectin and its hybrid) and a marketed product (N) of 4/24 mg artemether/ lumefantrine respectively. The control group was administered with 1 mL of distilled water. The mice were inoculated with 0.2 mL of *Plasmodium berghei* parasitized erythrocytes such that the 0.2 mL contained $1x10^7$ parasitized cells. After 72 h of inoculation blood samples were collected from the tail vein and thin films of the blood sample were made, fixed and viewed under the microscope using x 10 magnification.

$$\% \text{ Suppression} = \frac{DN - DP}{DN} X100$$

Where; DN= Parasitemia in negative control, DP= Parasitemia in positive control.

The prophylactic effects of the distilled water, D/W was less than that of the marketed product, N which in turn was less than that of the pectin formulated artemether-lumefantrine granules, M, which is also less than the hybrid formulated artemether-lumefantrine granules for oral suspension. This is in agreement with earlier report[10,11].

Limitations of the study

Formulation and analysis of the artemether-lumefantrine fixed-dose granules for oral suspension, and evaluation of the *in-vivo* activity of the formulated artemether-lumefantrine granules; some pharmaco-kinetic properties.

CONCLUSIONS AND RECOMMENDATION

The *in-vivo* studies carried out indicated that the percentage clearance and/or suppression of the optimized granules were higher than those of the marketed product, and more effective than earlier antimalarial agents such as quinine and chloroquine. Further animal studies are required to determine the suitability of the extracted pectin and/or its hybrids as suspending agents to be used to production of granules for oral suspension.

ACKNOWLEDGEMENTS

Our profound gratitude goes Mr. Amadi, Industrial Pharmacy Laboratory, Madonna University, Elele, and all the staff of Pharmaceutical Technology Laboratory, University of Port Harcourt, especially, Mr. Samson Bekweri, Mr. Madighiode Oghaaphemugh Pharmacology Department and Mr. Vite Toobari Monday of Basic Medicals, University of Port Harcourt. We acknowledge the Managing Directors/Chief Executive Officers of SABHEIK and EMZOR Pharmaceutical Companies.

AUTHOR'S CONTRIBUTION

Edwin AU: formulation development, determinations of the pharmacokinetic properties. **Emmanuel AU:** determination of the polymer properties of the extracted pectin, statistical analysis. Both authors reviewed the article and approved the final version.

CONFLICT OF INTEREST

None to declare.

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