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RESEARCH ARTICLE

DETERMINATION OF SOME PHARMACOKINETIC PROPERTIES OF ARTEMETHER-LUMEFANTRINE GRANULES IN ALBINO RATS

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Abstract

Aim and Objectives: Malaria is an infectious disease that is caused by plasmodium parasites which is rampant in Sahara Africa and children under 5 years of age are highly vulnerable to this infection by malaria. So the need for the formulation of dosage form for this population using naturally occurring excipients to replace imported ones being currently used by our local manufacturing industries in-order to formulate novel, readily available, affordable and effective antimalarial medicine for children.
Methods: Using the local excipients and its hybrid, the formulated artemether-lumefantrine granules for oral suspension were administered to albino rats, blood samples were collected at predetermined time 0, 1.5, 3, 6, 9, 12, 15, 18, 21, and 24 h respectively and drug contents; artemether-lumefantrine were determined within the stipulated period.
Results: Some pharmacokinetic parameters determined were; maximum concentration, C_{max}, time to reach the maximum concentration, T_{max}, half-life, $t_{1/2}$, area under the curve, AUC, and mean residence time, MRT, which were for artemether-lumefantrine were 3.9, 3.4, µg/L; 3.2, 6.0 h; 12.5, 14 h; 75.8, 168.5 µg/L.h; 24, 24 h respectively, for the marketed artemether-lumefanthrine granules for oral suspension.4.1, 3.2 µg/L; 1.4, 3.0 h; 3.0, undefined h, 67.0, 65.7 µg/L. h; 18, 18 respectively for hybrid formulated artemether-lumefantrine granules for oral suspension and 3.1, 3.8 µg/L; 2.5, 12.5 h; 4.8, 15 h; 20.2, 281.6 µg/L .h; 18, 18 respectively for the extracted pectin formulated granules.
Conclusion: Optimized formulated artemether-lumefantrine granules were superior to the marketed product in terms of pharmacokinetic values being closer to those of earlier workers.
Keywords: Area under curve (AUC), maximum concentration (C_{max}), mean residence time (MRT), pharmacokinetic, time to reach maximum concentration (T_{max}).

INTRODUCTION

Malaria infestation is very dangerous,though, the disease is preventable and curable, and caused by infected female anopheles mosquitoes. The parasites that are transmitted from person to person through the bites of the infected anopheles mosquitoes. There are five parasite species that transmit malaria in humans; *Plasmodium falciparum, P. malariae, P. vivax, P. ovule, P. knowlesi*, but, two of them pose the greater threat and these are *P. falciparum* and *P. vivax*. As reported by the World Health Organization, WHO that in 2019 about half of the world's population was at risk of malaria, but most of the cases and death occur in Africa[1]. It was estimated that 229 million of the world's population were infected in 2019, and 404,000 deaths were recorded and African continent was home to about 94% of the malaria infestation. Children under five years of age are the most vulnerable, which accounts for about 70% of all malaria deaths World Wide. Only six African countries accounted for more than half of all malaria cases World Wide; Nigeria 23, Democratic Republic of Congo , United Republic of Tanzania, Burkina Faso, Mozambique and Niger with 23, 11, 5, 4, 4, and 4% respectively. Artemether has half- life of about 2 h after oral administration. It has 95% protein bound. It has an active metabolite called dihydroartemisinin, DHA and a half- life of about 1 h[2]. Lumefantrine has elimination half-life of about 5 days. It may be attributed to its poor bioavailability. It has variable bioavailability and its absorption is highly influenced/increased by intake of fatty food. The pick

plasma concentration was reached after 10 h[3,4]. A pharmaceutical suspension is a two- phase system in which a finely divided solid drug particle is dispersed in a continuous phase of either solid, liquid or gas. These finely divided insoluble solid particles are in equilibrium with the saturated solution of the solid in continuous phase[5]. There are reasons why drugs are formulated as suspension. These include but not limited to the following; drugs in suspension are more readily bioavailable than drugs in tablet or capsule dosage form, poorly soluble or in-diffusible drugs are formulated as suspensions for uniform distribution of its medicament throughout the suspending medium and enhances the stability of drugs that are not stable in aqueous medium and such drugs are supplied in powdered forms for reconstitution at the time of dispensing. Pharmaceutical suspensions are made up of two major components; the active pharmaceutical ingredients and the excipients which are responsible for the pharmacologic effects and the stability of the dosage form respectively. In this case the active pharmaceutical ingredients are artemether and lumefantrine in fixed dose. The excipients include; suspending agents, surfactants, buffers, flavors/ sweeteners, colorants, diluents/fillers, preservatives, just to mention but a few[6]. The suspended drug material should not settle rapidly; the particles that do settle to the bottom of the container must not form a hard cake but should be rapidly re-dispersed into uniform mixture when the container is given a moderate amount of agitation. The suspension must not be too viscous to pour freely from the orifice of the bottle or to flow through a syringe needle for injections. Odor and color must be acceptable. Suspensions must have optimum physical, chemical and pharmacologic properties. Crystal growth, particle size distribution, specific surface area, changes of polymorphic forms do not occur sufficiently during storage to adversely affect the performance of the suspension as earlier reported in a previous study[7]. The ingredients must be readily obtainable that can be incorporated into the mixture with relative ease by the use of standard methods and equipment. The ingredients must be tolerable/non-hazardous according to earlier workers[5,6,8].

MATERIALS AND METHODS

Materials were procured and used without further purification; Conc. HCl, methanol, 0.05 mL syringes, centrifuge, capillary tubes, heparinized containers, marketed product, albino rats. Various formulations of granules formulated with pectin and its hybrid, *Plasmodium berghei* from Nnamdi Azikiwe University, Awka and distilled water,

Methodology

Artemether/lumefantrine granule for oral suspension was administered per oral to male wistar albino rats average 200±2g that were purchased from the animal house of university of Port Harcourt and allowed to acclimatize for two weeks; freely exposed to their feeds and water. Equal doses of the optimized formulated granule for oral suspension (G and M) and a marketed product were administered to three of the four groups and distilled water was administered to the fourth group respectively and monitored for 24 hours. Then blood samples were collected from the veins of the eye using capillary tubes at 0, 1.5, 3, 6, 9, 12, 15, 18 and 24 h in heparinized tubes and kept for 15–30 minutes. The collected blood samples were centrifuged at 4000rpm for 30 min and stored at -80^{o}C[9]. High performance liquid chromatography of the plasma was run as the standard, its compounds observed and noted the plasma samples for each of the groups were run in the HPLC and the chromatograms were printed and the concentration, peak values, retention time, and the area of the peaks were noted as reported[10]. The standard were determined respectively and was then used as a guide for the retention time determination which was used to determine the concentration of the drug component eluted at a particular time. The data obtained from the chromatogram was used to plot a time-concentration curve of the drugs; artemether and lumefantrine in the plasma using the optimized formulated granule for suspension M and G and the marketed product[11] and the results shown in Figure 1-Figure 3.

Ethical Approval: Issued on the 8th 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 retention time was determined from the standard preparation (Table 1). On administration of the optimized artemether/lumefantrine formulations, it was observed that the pharmacokinetic properties of the formulated granules are not the same. Artemether was released faster than lumefantrine. The pharmacokinetic properties of the granules are to some extent dependent on the functionality of the excipients; the extracted pectin and its hybrids respectively. This is according to earlier reports[12,13]. The maximum concentration of artemether and lumefantrine of sample N in the plasma, C_{max} were 3.9 and 3.4 µg/L respectively. The time of maximum concentration in the plasma, T_{max} for artemether and lumefantrine were 3.2 and 6.0 h respectively.

Table 1: Determination of the Retention time for Artemether and Lumefantrine in the formulated artemether-lumefantrine granule for oral suspension.

Parameter	Retention time (min)	Height (mAU)	Area (µg/L.h)	Concentration (µg/L)
Artemether	6.5	2977016	17870044	3.2999
Lumefantrine	12.0	2977016	32857914	3.3063

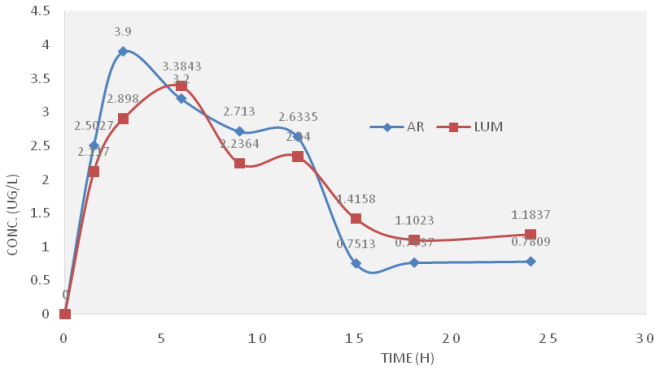

Figure 1: Concentration of formulation N in the plasma within 24 hours.

The half-life, $t_{1/2}$ which is the time for the concentration in the plasma to reach half quantity of artemether and lumefantrine were 12.5 and 14 h respectively. The area under the curve, AUC which determines dissolution and extent of absorption of a drug after its administration for artemether and lumefantrine were calculated to be 75.8 and 168.5 µg/L .h. The mean residence time, MRT which is the time the administered drug spends at the site of action for artemether and lumefantrine were determined to be 24 h respectively. Here the maximum concentrations of artemether and lumefantrine were 4.1 and 3.2 µg/L, and the time to reach this maximum concentrations, T_{max} were 1.6 and 3.0 h respectively, $t_{1/2}$ were 3.0 and undefined h respectively.

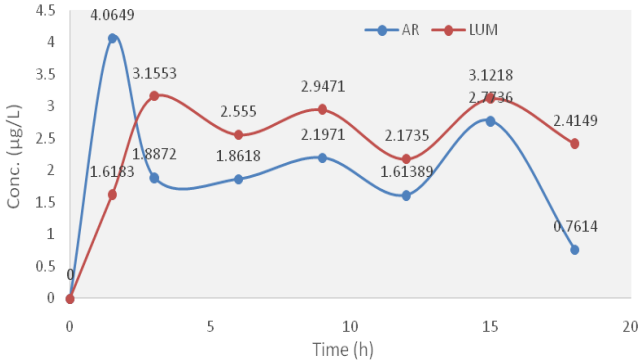

Figure 2: Concentration of formulation G in the plasma within 24 hours.

The AUC for artemether and lumefantrine were 67.0 and 65.7 µg/L.h respectively. The mean residence time, MRT was calculated to be 18 h for both artemether and lumefantrine. The maximum concentration in the plasma, C_{max} for artemether and lumefantrine in formulation M after its administration to wistar rats within 24 h were 3.1 and 3.8 µg/L respectively. The T_{max} for artemether and lumefantrine were 2.5 and 12.5 h respectively. The half-life of the administered dose for artemether and lumefantrine were 4.8 and 15 h respectively. The AUC which indicates the extent of drug dissolution in the systemic circulation were determined to be 20.2 and 281.6 µg/L.h for artemether and lumefantrine respectively.

The mean residence time, MRT which is the period an administered dose remains in the plasma was determined to be 18 h for artemether and lumefantrine respectively as reported in previous study[14,15].

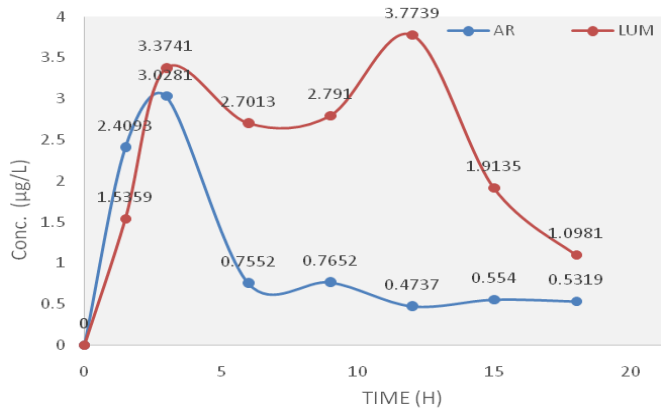

Figure 3: Concentration of formulation M in the plasma within 24 hours.

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 pharmacokinetic properties.

CONCLUSIONS AND RECOMMENDATION

Comparing some pharmacokinetic parameters of the optimized artemether-lumefantrine formulations, M & G with the marketed product, N, the $C_{max,}$ T_{max} and AUC of artemether were more appropriate than those of the marketed product according to previous workers The pharmacokinetic parameters such as C_{max}, T_{max}, $t_{1/2}$, AUC and MRT for the optimized formulated artemether-lumefantrine granules for oral suspension were more appropriate than the marketed product in terms of dissolution and subsequent systemic absorption as the said parameters are responsible for their bioavailability determinations. Further animal studies are required to determine the suitability of the extracted pectin and/or its hybrids as suspending agents to be used in the production of granules for oral suspension.

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AUTHOR'S CONTRIBUTION

Edwin AU: formulation of the artemether-lumefantrine fixed dosage form, analysis and the determinations of the pharmacokinetic properties. **Emmanuel AU:** determination of the polymer properties of the extracted pectin and its hybrids and the entire statistical analysis of the work. Both authors reviewed the article and approved the final version.

DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

CONFLICT OF INTEREST

None to declare.

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