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Science Article

EVALUATION OF THE QUALITY OF ARTHEMETER-LUMEFANTRINE BRANDS USED IN THE TREATMENT OF P. FALCIPARUM MALARIA IN CHILDREN BELOW FIVE YEARS IN DELTA STATE

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Abstract

Background: There have been records of widespread resistance with the use of mono-therapy in the management of malaria. Nigeria initiated the use of Arthemisinin-based combination therapy (ACT) in 2005 following the WHO recommendation. Globally and in particular Nigeria, there is high risk of resistance to the ACTs due to the faking, act of counterfeiting and substandard drugs. This can pose serious problem that needs redress, hence the need for this study to check for any substandard or counterfeit Arthemeter-Lumefantrine tablets in Delta State.

Objective: The objective was to assess the quality of 5 different brands of ACTs containing arthemeter 20mg and lumefantrine 120mg packed by 6 or12 tablets for malarial treatment for children below 5 years.

Methods: A total of five different brands of Arthemeter-Lumefantrine were purchased from retail outlets in major cities of the state and qualitative tests which include general appearance, friability, weight uniformity, disintegration, hardness, diameter were carried out following the United State and British Pharmacopeia test procedures while dissolution test was carried out using the Copley dissolution test apparatus, England.

Results: The qualitative test for the 5 different brands showed that all had uniform weight, hardness were within range of 1.9 – 7.1 KgF, thickness was within the range of 3.7 – 4.5 mm while the diameter was within the range of 9 – 10 mm. Result for friability showed that brands CB, LT, and LM met required standard while GV and CM did not. The tablets disintegrated at a prescribed limit which was in the range of 1.68 – 45.88 secs. For dissolution of the five brands, LM released more than 50%, CB released 50%, GV released 34.1% and CM released 25.4% at 60 minutes using lumefantrine as the experimental marker.

Conclusion: From the results of this study, LM is the optimized brand as it passed the various test for quality with values within specifications.

Keywords: Arthemeter-Lumefantrine, ACTs, brands, substandard or counterfeit, fake

Introduction

There has been report of widespread resistance with the use of mono-therapies in the management of malaria. In 2005, Nigeria initiated the use of Arthemeter-based combination therapy (ACT) following the World Health Organization (WHO) recommendation[1]. Globally and in particular Nigeria, there stands a high risk of development of resistance to the ACTS due to several reasons. The relatively high cost of these antimalarials has made their manufacture a lucrative venture for pharmaceutical industries; a situation that has led to the proliferation of diverse brands on the market. This has led some unscrupulous people to indulge in the manufacture of substandard and falsified brands[2,3,4]. The WHO acknowledges the difficulty that this situation presents to the quality assurance of antimalarials on the market, especially in developing countries where enforcement of laws regarding manufacture, importation and distribution of medicines is relatively lax. Tabernero *et al.*[5], reported that the quality of antimalarial drugs are not available for the majority of malaria endemic countries notably Nigeria. *P. falciparum* resistance has been confirmed in several parts of South East Asia, where the problem of counterfeit medicines is well organized[6]. The manufacture, distribution, and use of poor quality medicines (degraded, substandard and counterfeit) are major factors in the development of resistance. There has been considerable global controversy and tensions among public health stakeholders regarding the definitions of categories of poor quality medicines. The core issues of safety, quality, and efficacy of medicines was diverted following the adoption of the operational definition of counterfeit medicines by WHO in 1992 and later revised in 2008 by IMPACT[7,8]. The problem led to the WHO 2010 proposal that until consensus is reached, medicinal products produced or distributed with the intent of fraud could be described as substandard/spurious/falsely labeled/falsified/counterfeit medicinal drugs (SSFFC)[9].

However, this lumping of all poor quality medicines together has been described as creating a misleading impression. New proposals suggest that substandard medicines should be separated from counterfeit products and that the term "counterfeit" should be excluded from the definitions for the purpose of international cooperation[10]. Thus, substandard medicines are defined as pharmaceutical products produced by legitimate manufacturers (originator and generic) which do not meet their quality standards and specifications[11]. Both substandard and falsified medicines pose a serious threat to public health. In as much as the ACTs remain the most effective treatment for uncomplicated *P. falciparum* malaria, it is extremely important to monitor the quality of the ACTs as part of the measures to curtail the spread of ACT-resistant parasites to the malaria endemic African region. We undertook to evaluate the quality of arthemeter-lumefantrine brands used in the treatment of malaria in children below the age of five years in Delta State with comparing them to British Pharmacopeia standards.

Methods/Materials

Sampling

All the brands sampled are in solid dosage forms commonly employed for the treatment of uncomplicated *P. falciparum* malaria in children below 5 years in Delta State. All 5 brands were collected from retail outlets in major cities of the state, this is because majority of consumers usually buy from retail outlets more than from wholesalers.

Another reason for purchasing most of the samples from retail outlets instead of wholesale outlets was to cut down on cost. For example, if three packets of a medicine containing ten tablets each were enough for chemical analysis, it was cheaper to purchase these three individual packets from a retailer than buy a whole box of the same medicine containing about twenty packets from a wholesaler. This strategy enabled us to buy more samples that belonged to different batches of the same medicine. The various brands with their specifications are shown in the Table 1

Table 5: Socio-demographic characteristics of patients

Specification	Brands				
	GV	CB	CM (d)	LM	LT (d)
Batch No	P082167	GIAFK003	K0123	ID62001	E1AFK020
Mfg Date	10/2016	02/2017	02/2016	05/2016	08/2015
Exp Date	09/2018	01/2019	01/2018	04/2019	07/2017
NAFDAC Reg No.	B4 -0591	A4 -7524	A4 -1680	A4 -4845	A4 -4238

Key: (d) – dispersible brands

Equipment

Analytical balance (Shimazu Philippines Manufacturing INC. Japan), Concentrated hydrochloric acid (BDH, Chemical Ltd. Pools, England), distilled water (prepared in the Department of Pharmaceutics), UV spectrophotometer (G. Bosch, Germany), hardness, thickness and diameter tester, (Veego Instrument Cooperation; model no: VDGTABOI, Mumbai, India), friabilator (Veego tablet friability test apparatus; model no: VFT-DV), Manesty tablet disintegration test unit (Manesty machines Ltd. Liverpool 24 made in England; model no: TD29T176), Methanol (HPLC grade) (Guangdong Guanghua Sci-Tech, China), acetonitrile (Guangdong Guanghua Sci-Tech, China), High Performance Liquid Chromatography (HPLC).

Quality Control of Tablets

General Appearance: The general appearance of the tablets was evaluated such as size, shape and organoleptic properties such as odour, colour and texture.

Weight Uniformity Test

Twenty (20) tablets were randomly selected and weighed using the analytical weighing balance (Shimadzu analytical weighing balance; model no; ATY224, Philippines) and the average weight calculated.

Hardness, Thickness and Diameter Tests

Six tablets were randomly selected for these three tests. The machine (Veego Instrument Cooperation; model no: VDGTABOI, Mumbai, India) was operated to measure for each of the tests.

The weight of each of the six (6) tablets was entered on the machine display screen and each tablet was placed vertically in the tablet compartment to allow the measurement of the thickness and diameter of the tablet. Then, the tablet in the compartment was placed horizontally to measure the pressure at which the tablet cracked. The values of the tests for each of the brands were recorded.

Friability tests

Ten (10) tablets were weighed all together and the values were recorded. The weighed tablets were then subjected to the combined effect of abrasion and shock in a friabillator (Veego tablet friability test apparatus; model no: VFT-DV) at 25rpm for 4 min. Tablets were dusted using a soft muslin cloth and the weight recorded. The values were then recorded for each brand. The friability of the five brands was determined by using Equation 1

$$f = \frac{W_i - W_f}{W_f} \times 100\% \quad \text{..... Eq 1}$$

Where;
f = Friability
W_i = initial weight before friability
W_f = Final weight of ten tablets after friability.

Disintegration Test

A disintegration test equipment was used (Manesty tablet disintegration test unit, Manesty machines Ltd. Liverpool 24 made in England; model no: TD29T176). The disintegration medium used was distilled water maintained at 37°C±1. One tablet was placed in the six disintegrating baskets and the equipment was switched on to allow the baskets move up and down in the disintegration medium so that the tablets are constantly agitated. Disintegration was complete when all the particles from the tablet passed through the mesh. The time taken for each tablet to break up and pass through the screen was recorded, for a conventional tablet is within 30 min.

Dissolution Test

The stirred beaker method was employed using Copley dissolution test apparatus, England. A tablet from each batch was placed in the cylindrical basket. The basket containing the tablet was then clamped and placed in a beaker containing 900 ml of the dissolution medium (0.1N HCl) and maintained at 37°C±1. The medium was then stirred at 100 rpm. Using a 5ml syringe, samples of the leaching fluid were collected at predetermined time intervals into sample bottles. The samples were then assayed for drug content using a UV/VIS Spectrophotometry at a wavelength of 350 nm.

Results

A total number of seven qualitative tests were carried out to assess the quality of the five (5) different brands of arthemeter – lumefantrine used in treating *P. falciparum* malaria in children below five years. The qualitative tests are presented in Table 1.

Table 1: Qualitative tests on Brands of Arthemeter-Lumefantrine

Qualitative Tests	GV	CB	CM[(d)]	LM	LT[(d)]
Thickness	4.33 ± 0.10	4.49 ± 0.05	4.30 ± 0.03	3.62 ± 0.14	4.38 ± 0
Disintegration time (s)	9.09 ± 1.65	45.88 ± 4.62	23.25 ± 1.85	1.68 ± 0.24	5.62 ± 0.13
Diameter (mm)	10.35 ± 0.04	9.74± 0.06	9.11 ± 0.02	7.10 ± 0.22	10.34 ± 0
Content Uniformity of Lumefantrine (%)	88.2	105.0	112.8	101.0	112.4
Friability (%)	4.82	0.43	3.15	0.54	0.45
Hardness (KgF)	1.99 ± 0.53	5.61 ± 0.30	4.10 ± 0.31	7.10 ± 0.22	2.91 ± 0.26
Weight Uniformity	0.29 ± 0.01	0.36 ± 0.01	0.29 ± 0.01	0.35 ± 0.01	0.30 ± 0.01

Key: [(d)] – dispersible brands

Cumulative Release Curve

The release pattern of the different brands of arthemeter-lumefantrine is shown in Fig. 1:

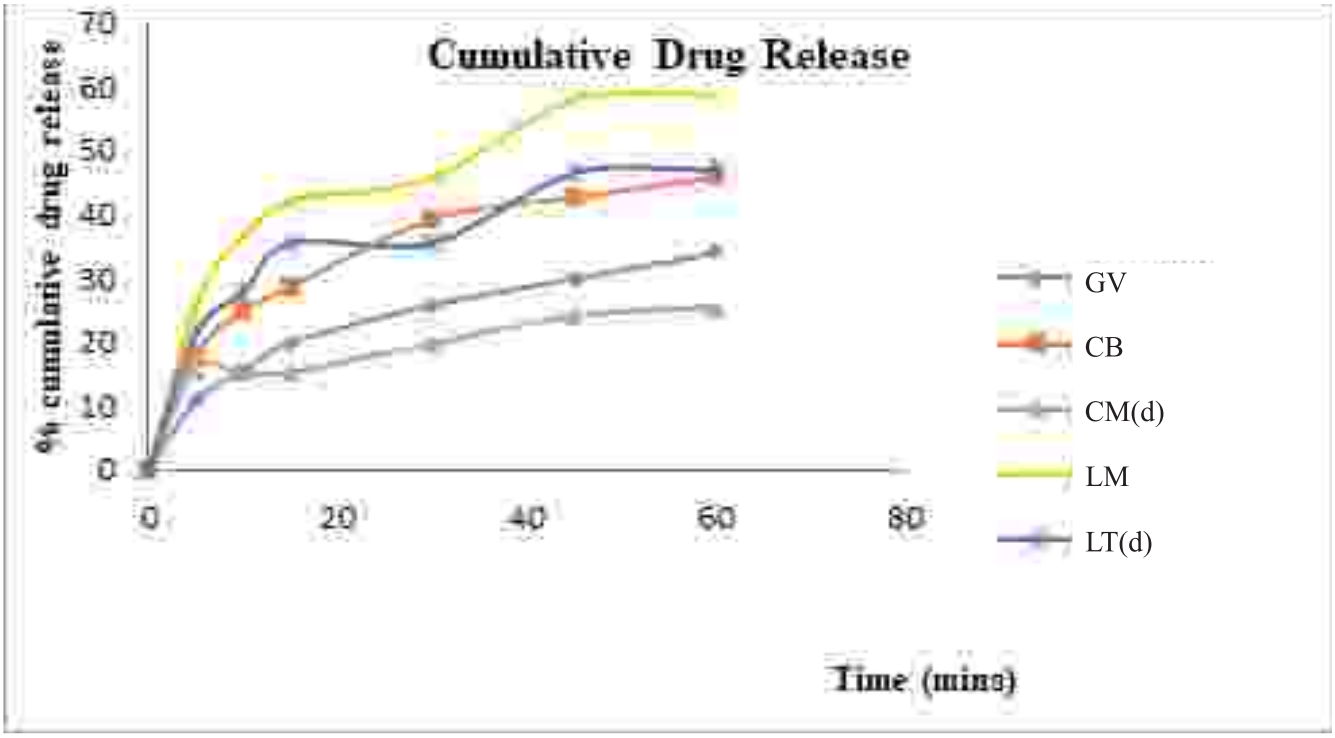

Fig. 1: Percentage Cumulative Drug Release Curve of the Brands of ACTs

Discussion

The weight variation test was carried out in order to ensure uniformity in the weight of tablets in a batch. All tablet brands of ACT passed weight variation test as the percentage weight variation was within British Pharmacopoeia (BP)[13] which allowed ±7.5% deviation for average weight of 80-250 mg and ±5% for more than 250mg. The weight of all the tablets was found to be uniform with low standard deviation values indicating uniformity. Furthermore, the British Pharmacopoeia (BP)[13] official limit for weight uniformity of tablets is that the deviation of the individual tablet from the average weight should not exceed the limit of ±7.5. Thus, the result of this study is consistent with the B.P[13] official specification and it shows that the weight uniformity of the tablets is in compliance with qualitative standards required of good tablets. This is in concert with the study done by James *et al*[14] which recorded a percentage deviation of less than 10%. Tablets with uniform weights are expected to have uniform active medicaments. This avoids under-dosage or over-dosage during treatment with the same batch of tablets.

The hardness was found to be in the range of 1.9 kgF to 7.1 kgF for the tablet brands indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. Thickness in all the brands ranges from 3.7 mm to 4.5 mm and diameter range of 9mm to 10mm. The result further revealed that only brand CB (5.61 KgF), $CM^{(d)}$ (4.10 KgF) and LM (7.1 KgF) met the BP[13] specifications of 4-14 KgF and this is in contrast to that obtained from samples of arthemeter-lumefantrine by El-Duah *et al*.[14] which was 11.2 KgF. The crushing strength measures the tensile strength of the tablets to resist external forces or humidity.

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Not all the tablet brands meet the BP limits for friability. CB, LT[(d)], and LM passed the friability test with less than 1% friability which meets with the BP[13] Specifications for friability test of <1%. Study by James *et al*[14] reported similar friability of less than 1% in AL tablets. Brands CM[(d)] and GV both failed the friability test with % friability above 1%. This means that the brand of CB, LT[(d)], and LM would be able to withstand abrasion during packaging and handling including movement of the drug from place to place. Brands CM[(d)] and GV on the other hand cannot be able to withstand these abrasions.

The results for disintegration time of all the brands of ACT were found to be within the prescribed limits and satisfy the criteria of dispersible and non-dispersible tablets. The Disintegration time of all batches was within range of 1.68 - 45.88 seconds. The standard for disintegration time of dispersible tablets should not be more than 3 minutes and all the brands including the non-dispersible met with this specification[13]. From the result it can be deduced that brand LM gave the lowest rate of disintegration time of 1.68 seconds than brand CB which gave the highest rate of disintegration time of 45.88 seconds among the various brands tested. Similar studies by James *et al*[14] reported that the disintegration time of AL tablets was less than 900 seconds (15 minutes) which is in tandem with this study.

LM was the only brand of ACT that was able to release more than 50% of the drug into solution at 60 minutes. CB and LT[(d)] were able to release close to 50% at 60 minutes. Meanwhile, GV and CM[(d)] gave a very poor percentage release of about 34.1% and 25.4% respectively. BP Specifications instructs that a non-coated tablet must release up to 70% of the drug at 45 minutes. Thus the non-dispersible brands of ACT used for this experiment failed the BP Specifications for drug release profile. Furthermore, dispersible brands used in this study LT[(d)] and CM[(d)] failed the BP specifications for drug release profile.

Conclusion

The different brands of ACT used in this study passed the BP specifications for dispersible tablets although non-dispersible brand, LM could be referred to as the optimized brand since it was able to release over 50% of the lumefantrine at 45min.

Recommendations

One of the point to consider in choosing a solvent medium for a dissolution test is the solubility profile of that drug in that solvent medium. The type of analysis should also be considered before running a dissolution test to ensure that the type of analysis is able to give accurate results. Instruments used for analysis should also be considered. High Performance Liquid Chromatography (HPLC) and use of a Double Beam Spectrophotometer should be encouraged to ensure accuracy of result.

Limitations

The failure experienced in this dissolution test may be due to a number of factors which may include dissolution medium, type of analysis carried out and instrument used. The dissolution medium used may not be able to absorb a large amount of the drug which depends on the solubility profile of the drug in the solvent system used for the dissolution test.

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