J Vector Borne Dis 49, September 2012, pp. 131–139

Substandard artemisinin-based antimalarial medicines in licensed retail pharmaceutical outlets in Ghana

M. El-Duah & K. Ofori-Kwakye

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana

ABSTRACT

Background & objectives: The artemisinin-based antimalarial medicines are first line medicines in the treatment of severe and uncomplicated falciparum malaria. Numerous brands of these medicines manufactured in various countries are available in the Ghanaian market. The study was aimed at evaluating the authenticity and quality of selected brands of artemisinin-based antimalarial medicines marketed in Ghana.

Methods: In all, 14 artemisinin-based antimalarial medicines were purchased from pharmacies (P) and licensed chemical shops (LCSs) in the Kumasi metropolis, Ghana. Simple field tests based on colorimetry and thin layer chromatography were employed in determining the authenticity of the samples. Important quality assessment tests, namely uniformity of mass, crushing strength, disintegration time, and the percentage content of active pharmaceutical ingredients (APIs) were determined.

Results: All the brands tested contained the stipulated APIs. Artesunate tablet AT2 failed the uniformity of mass test while artesunate tablets AT3 & AT4 as well as amodiaquine tablets AM4 & AM6 failed the crushing strength test. All the six artemether-lumefantrine tablet brands passed the uniformity of mass, crushing strength and disintegration tests. Only artemether-lumefantrine tablet brand AL1 contained the correct amount of the drugs. The other 13 artemisinin products contained either a lower (underdose) or higher (overdose) amount of the specified drug. Artesunate monotherapy tablets were readily available in pharmacies and licensed chemical shops.

Interpretation & conclusion: All the artemisinin-based medicines tested (except AL1) were of substandard quality. The results demonstrate the need for continuous monitoring and evaluation of the quality of artemisinin-based antimalarials in the Ghanaian market. Also, the practice of artemisinin antimalarial monotherapy is prevalent in Ghana. Determined efforts should, therefore, be made to eradicate the practice to prevent the development of resistance to the artemisinins.

Key words Artemisinin-based combination therapy; artesunate monotherapy; counterfeit antimalarials; substandard antimalarials

INTRODUCTION

Artemisinin-based antimalarial medications are highly potent and effective antimalarials used in the treatment of uncomplicated and severe falciparum malaria. In malaria endemic countries, such as those in sub-Saharan Africa, artemisinin-based combination therapies (ACTs) are recommended for use as the first line medication for uncomplicated malaria[1]. The sources of supply, distribution and quality of artemisinin-based antimalarials available for use in various countries have recently engaged the serious attention of researchers. This is because of poor quality antimalarials, either as counterfeit or substandard artemisinins, have been reported in different parts of the world. This could have serious implications on malaria chemotherapy.

Counterfeit medicines are drugs deliberately and fraudulently mislabeled with respect to identity and/or source. These occur with both branded and generic products and may include products with the correct ingredients or with the wrong ingredients or without active ingredients or with insufficient active ingredients or with fake packaging[2]. Substandard drugs, on the other hand, are genuine medicines which upon laboratory analysis fail the specifications claimed by the manufacturer due to poor manufacturing technology, poor storage and transportation[3]. The WHO has estimated that 25% of all the medicines in developing countries are counterfeit and this figure is projected to be as high as 40 to 50% in Nigeria and Pakistan[4]. Counterfeit or substandard artemisinin antimalarials may cause serious injury (as they often contain toxic chemicals) or death to patients because of mistreatment[5]. These may also cause a reduction in public confidence in medicines which could result in reduced intake of potentially life-saving medicines[6]. Counterfeiting may serve as a strong disincentive to Research and Devel-

opment industries to invest in future innovation in malaria research. Also, exposure of malaria parasites to sub-therapeutic concentrations of artemisinins may result in development of parasites which are resistant to the drugs and consequently, result in treatment failure.

In Africa, the availability of substandard and possibly counterfeit artemisinin-based antimalarials has been reported in several countries. A study in Nigeria reported significant differences in the dissolution profiles of nine brands of artesunate tablets, with one brand having a particularly low dissolution rate which was likely to cause poor bioavailability of the product[7]. In Ghana, a recent study found that the content of artesunate in 17 brands of artesunate tablets varied from 47.9 to 99.9% of the labeled amount and while 6 (35.3%) of the artesunate tablet brands passed the International Pharmacopoeia content uniformity test, 11 (64.7%) failed the test[8]. Another study in Ghana reported that only 14 (28.6%) out of 49 samples of different dosage forms of artemisinins analysed by semi-quantitative TLC assay had values likely to meet pharmacopoeial specifications[9].

A study of the quality of various antimalarials in Burkina Faso showed one artemisinin product being substandard[10]. The presence of counterfeit and substandard artemisinin-derivative antimalarials has also been reported in Kenya and Democratic Republic of Congo[11]. In a study using validated HPLC-UV methods, the researchers reported that 9 out of 24 samples failed the European Pharmacopoeia requirements of 95–105%, with seven samples being underdosed and two being slightly overdosed. The availability of counterfeit artesunate and counterfeit dihydroartemisinin has also been reported in Cameroon and Tanzania[12]. In a study of the quality of antimalarials including artemisinins, which involved the major cities of six countries, namely Ghana, Kenya, Nigeria, Rwanda, Tanzania and Uganda, 35% of the samples analysed were found to be substandard[13]. In Asia, a field survey of antimalarials in several South East Asian countries reported that 53% of artemisinin-based antimalarials contained incorrect amounts of the active ingredients[6]. Other studies have also cited the distribution and use of counterfeit and substandard artemisinins in South East Asia[14–16].

In Ghana, different artemisinin-based antimalarial medications in varying dosage forms and strengths, imported and locally manufactured, are readily available at pharmacies and chemical shops. The lack of the requisite technical and human resources means that monitoring, evaluation and control of the drug supply chain is inadequate. Poor quality antimalarials are, therefore, likely to enter the drug supply chain which needs to be screened and eliminated.

The aim of the study was to determine the authenticity and quality of a number of artemisinin-based medications purchased from pharmacies and licensed chemical sellers' shops in Ghana. The results of the study would demonstrate whether the products are of good quality or poor quality (substandard or counterfeit).

MATERIAL & METHODS

Artesunate, amodiaquine, artemether and lumefantrine powders were obtained from Ipca Laboratories Ltd. (Mumbai, India). Fast Red TR salt (1, 5-Naphthalenedisulfonate salt, reagent grade) was obtained from Acros Organics, New Jersey, USA, and dehydrated ethanol was obtained from BDH Ltd., UK. Sodium hydroxide, acetic acid, methanol, 2,4-dinitrophenylhydrazine (Brady's reagent, DNP), potassium iodide, ethyl acetate, hydrochloric acid, acetic anhydride, glacial acetic acid, perchloric acid, potassium hydrogen phthalate and Oracet blue indicator, Dragendorff's reagent and vanillin/sulphuric acid reagent were obtained from the Chemical Store of the Departments of Pharmaceutics and Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST, Ghana. Distilled water used was freshly prepared.

Sampling of antimalarials

The study was conducted in the Kumasi metropolitan area of Ghana (total area: 254 km^2; population: 1,625,180). The area was chosen because of its high population density and due to its high reputation as a hub for illegal drug trade activities. A female sampler who presented herself as an ordinary customer, purchased the drugs (1 February to 5 March 2010) from licensed pharmaceutical outlets selected to ensure a wide geographical spread. Five brands of artesunate and amodiaquine combi-pack tablets and two brands of artesunate monotherapy tablets were purchased. The combi-packs contained artesunate tablets and amodiaquine tablets packaged as co-blisters. Six brands of artemether-lumefantrine co-formulated tablets and one brand of artemether injection were also purchased. A dosage unit of artemether-lumefantrine tablets contains artemether (20 mg) and lumefantrine (120 mg); however, one sample contained artemether (40 mg) and lumefantrine (240 mg). The drugs were selected for study as artesunate/amodiaquine and artemether-lumefantrine are recommended as first line medicines for uncomplicated malaria by Ghana Health Services, while artemether injection is used for severe malaria. Artesunate monotherapy tablets were sampled to determine its availability in licensed premises for use in malaria treatment. The packaging of the

various brands of antimalarials was examined for any features of illegal prints. No further checks were done to distinguish the genuine products from possible counterfeits. The characteristics of the artemisinin-based antimalarial samples are shown in Tables 1 and 2.

Uniformity of mass, crushing strength and disintegration tests

The mass uniformity of artesunate, amodiaquine and artemether-lumefantrine tablets was determined as the mean and standard deviation of 20 randomly selected tablets. Crushing strength of 10 randomly selected tablets was determined using a hardness tester (DBK Instruments, India). The disintegration time of six randomly selected tablets was determined using Erweka ZT4-4 disintegrating apparatus (Heusenstamm, Germany) with distilled water as the medium and immersion fluid maintained at 37 ± 2°C.

Assessment of authenticity of artesunate tablets

Qualitative analysis of artesunate tablets was performed using both colorimetry and thin layer chromatography (TLC). For the colorimetric analysis, a previously validated analytical procedure was adopted[17]. Approximately, 1% of the test artesunate tablet was scraped into a clean tube and labeled with the test number. An equivalent mass of artesunate powder was poured into a clean test tube and labeled as positive control. A clean test tube was left empty and labeled as negative control. NaOH (0.5 ml of 1M) was added to all the test tubes and shaken gently and allowed to stand for 5 min. Acetic acid (1 ml of 1.1M) was added to all the test tubes and shaken gently after which 0.5 ml of 5 mg/ml Fast Red TR salt solution was added to the tubes and mixed gently. The content of each tube was observed after 5 min for any colour change. Formation of a yellow colouration indicates the presence of artesunate in the sample. In order to interpret the test, the positive control must turn yellow and the negative control must remain colourless. A previously reported technique was used in the TLC analysis of artesunate tablets[18]. A quantity of pure artesunate powder was dissolved in 0.2 ml of methanol and the solution was mixed thoroughly by manual shaking and then placed in an ultrasonic bath for 30 sec. The artesunate tablet was pulverized with a pestle in a mortar and 2 ml of methanol was added. The mixture was placed in an ultrasonic bath for 30 sec for solubilization to take place. The mixture was left on the bench for about 5–10 min to encourage sedi-

Table 1. Characteristics of artesunate/amodiaquine combi-pack and artesunate monotherapy tablets sampled

Sample code	Country of origin	Strength (AT/AM) mg	Date of manufacture	Expiry date	FDB registration
Artesunate (AT)/Amodiaquine (AM)					
AT1/AM1	Ghana	100/300	2/09	2/11	Yes
AT2/AM2	India	50/153.1	6/08	5/11	NA
AT3/AM3	Ghana	100/300	9/09	9/12	NA
AT4/AM4	India	100/300	8/09	7/12	NA
AT5/AM5	Ghana	100/306	8/09	1/11	NA
Artesunate monotherapy tablets					
AT6	Ghana	200/–	4/09	4/12	NA
AT7	China	50/–	11/09	10/12	NA

FDB = Food and Drugs Board, Ghana; NA = Not available.

Table 2. Characteristics of artemether-lumefantrine tablets and artemether injection sampled

Sample code	Country of origin	Strength (ART/LUF) mg	Date of manufacture	Expiry date	FDB registration
AL1	Switzerland	20/120	1/10	12/11	NA
AL2	India	40/240	8/10	7/12	NA
AL3	India	20/120	11/09	10/12	Yes
AL4	Ghana	20/120	9/10	8/13	NA
AL5	India	20/120	3/10	2/12	NA
AL6	India	20/120	5/10	4/12	NA
ARTJ*	India	80 mg/ml	7/10	6/13	NA

*Artemether injection; ART = Artemether; LUF = Lumefantrine; FDB = Food and Drugs Board, Ghana; NA—Not available.

mentation. The individual samples in methanol were each mixed thoroughly and a small quantity of each was applied in a graphite pencil drawn circle or spot on the TLC sheet. Brady's reagent was dropped on each spot. The reaction was allowed to proceed at room temperature and observed for any colour change.

Determination of percentage content of artesunate tablets

A previously reported method[17] with minor modifications was used[8].

Assay of amodiaquine tablets

The assay of amodiaquine tablets in the artesunate/amodiaquine combi-packs was performed according to the United States Pharmacopoeia procedure[19].

Assessment of authenticity of artemether in artemether injection and artemether-lumefantrine tablets

The authenticity of artemether in artemether injection and artemether-lumefantrine tablets was determined using basic official tests[20]. Test A: A quantity of the powdered artemether-lumefantrine tablets equivalent to about 80 mg of artemether, 40 ml of dehydrated ethanol was added. The solution was shaken well to dissolve and filtered. Half of the filtrate was evaporated to about 1 ml and 100 mg of potassium iodide was added and heated on a water bath for about 5 min. A yellow colouration signifies the presence of artemether; and Test B: The remainder of the filtrate was evaporated to about 5 ml. A few drops of this solution were placed on a white porcelain dish and 1 drop of vanillin/sulphuric acid was added. Development of a pink colour signifies the presence of artemether. The contents of one ampoule of artemether injection equivalent to about 30 mg of artemether was added 6 ml of dehydrated ethanol and shaken well to dissolve. A few drops of this solution were put on a white porcelain dish and 1 drop of vanillin/sulphuric acid added. Development of a pink colour is expected if artemether is present.

Assessment of authenticity of lumefantrine in artemether-lumefantrine tablets

Qualitative analysis of lumefantrine in artemether-lumefantrine tablets was carried out using basic identity tests[20]. A quantity of powdered tablets of artemether-lumefantrine equivalent to 10 mg of lumefantrine in a test tube was added 5 ml of ethyl-acetate. A few drops of 1M hydrochloric acid solution was added. The solution was stirred, warmed and filtered. To a portion of the test solution, a few drops of Dragendorff's reagent was added. Formation of an orange precipitate implied the presence of an alkaloid. Another sample of powdered tablets equivalent to 10 mg of lumefantrine, 5 ml of methanol was added and shaken well to dissolve. To the solution 20 mg of potassium permanganate was added and boiled for about 1 min. The solution was filtered and a few drops of 2, 4-dinitrophenylhydrazine solution (Brady's reagent) was added and shaken. A positive test for lumefantrine was observed if an orange precipitate was produced.

Determination of artemether content in dosage forms

A previously reported method [21] was employed in the determination of artemether content in artemether injection and artemether-lumefantrine tablets.

Determination of lumefantrine content in artemether-lumefantrine tablets

The percentage content of lumefantrine in artemether-lumefantrine tablets was determined by non-aqueous titration using perchloric acid as titrant and glacial acetic acid/acetic anhydride as solvent, and the end point determined potentiometrically[22].

RESULTS

The country of manufacture of the artemisinins, as indicated on the product labels, was Ghana, India, China and Switzerland. Only two of the products sampled 2/14 (14.3%) had the registration number of the Food and Drugs Board (FDB), the official drug regulatory body in Ghana. The remaining products 12/14 (85.7%) had no FDB registration numbers. The shelf-life of the samples ranged between 2 to 3 years. Two brands of artesunate monotherapy tablets (AT6 & AT7) were available at several licensed retail pharmacies and chemical shops. All the samples purchased had at least 6 months left on the shelf-life and analysis was carried out before the due expiry dates. Physical examination of the product packagings did not provide any indication that the samples were counterfeit or substandard.

All the artemisinin-based antimalarial tablets, except artesunate tablet brand AT2, passed the British Pharmacopoeia uniformity of mass test. The tablet mass for 50, 100 and 200 mg strength artesunate tablets was 281.5–296.3 mg (n = 2), 207.4–354.9 mg (n = 4) and 603.1 mg (n = 1), respectively. The tablet mass for 153.1 and 300 mg strength amodiaquine tablets was 308.4 mg (n = 1) and 481.7–592.5 mg (n = 4), respectively. The tablet mass for artemether-lumefantrine tablets of strength 20/120 and 40/240 mg was 242.7–341.1 mg (n = 5) and 580 (n = 1), respectively. All the tablets disintegrated in aqueous me-

dium in <15 min (range: 12–590 sec) and thus passed the British Pharmacopoeia disintegration test.

Artesunate tablet brands AT1, AT4, AT5 & AT7 had crushing strength >39.2 N (> 4 kgf) and were considered to be satisfactory while AT2 & AT3 had a crushing strength of 27 N & 23 N (< 4 kgf), respectively and can be described as soft tablets. AT6 was a coated tablet and thus had a considerably high crushing strength of 169 N. Amodiaquine tablet brands AM1, AM2 & AM4 had good crushing strength (58.6–123.5 N) while AM3 & AM5 are considered to be soft tablets as they had suboptimal crushing strength of 35 & 36 N, respectively. All the six artemether-lumefantrine tablet brands had satisfactory crushing strength (46.7–112.4 N).

Qualitative tests designed to assess the authenticity of artesunate tablets using Fast Red TR dye technique led to the formation of yellow coloured products of varying intensity for all seven samples (Table 3 & Fig. 1). This signifies the presence of artesunate in the tablets. Also, TLC spots of artesunate tablet samples yielded orange to dark pink colours when sprayed with DNP confirming the presence of artesunate in the samples (Table 4 & Fig. 2). Colorimetric tests on six artemether-lumefantrine tablet brands yielded coloured products of varying intensity (pink for artemether, orange for lumefantrine), indicating the presence of artemether and lumefantrine in the co-formulated tablets (Tables 5 & 6). The qualitative tests showed that the tablets contained the specified active pharmaceutical ingredient(s) and were thus not counterfeits.

Quantitative evaluation tests showed that all the artesunate tablet brands did not contain the stipulated

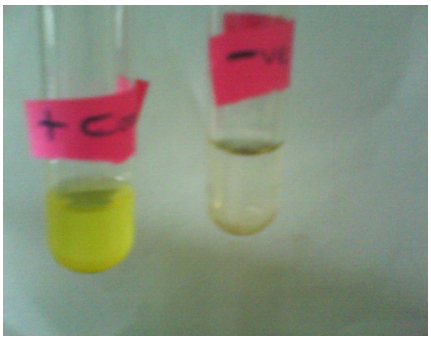

Fig. 1: Test for authenticity of artesunate tablets by colorimetry showing positive and negative controls. + = Pure artesunate powder showing yellow colouration (positive control); — = No artesunate present with sample showing no yellow colouration (negative control).

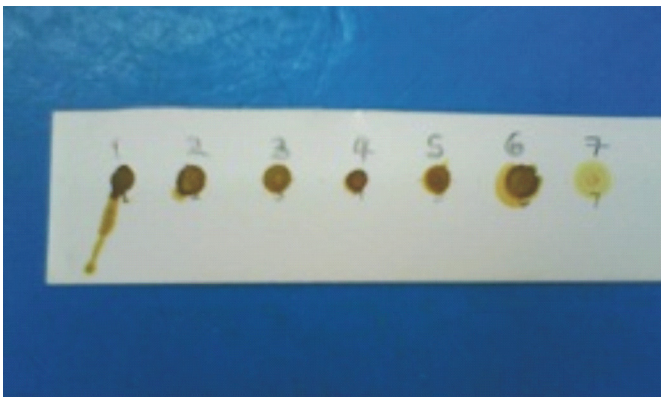

Fig. 2: Thin layer chromatography plate spotted with artesunate tablet samples. 1 = positive control (pure artesunate), 2–6 = Artesunate tablet brands AT1–AT5, and 7 = Negative control (No artesunate) showing no colour change from orange.

Table 3. Determination of authenticity of artesunate tablets by colorimetry

Test sample	Observation	Inference
Pure artesunate (positive control)	Clear before addition of FRTR solution. Yellow colour developed 5 min after addition of FRTR	Artesunate present
AT1, AT2, AT3, AT4, AT5, AT6 & AT7	Clear before addition of FRTR solution. Yellow colour developed 5 min after addition of FRTR solution	Artesunate present
No sample (negative control)	Clear before and after the addition of FRTR solution	Artesunate absent

FRTR—Fast Red TR salt.

Table 4. Determination of authenticity of artesunate tablets by thin layer chromatography

Test sample	Observation	Inference
Pure artesunate (positive control)	Orange to dark pink/rust/brown	Artesunate present
AT1, AT2, AT3, AT4, AT5, AT6 & AT7	Orange to dark pink/rust/brown	Artesunate present
No sample (negative control)	Orange to dark pink/rust/brown	Artesunate absent

Table 5. Test for authenticity of artemether in artemether-lumefantrine tablets and artemether injection

Test sample	Observation (Test A)	Observation (Test B)	Inference
Pure artemether powder (positive control)	Yellow colour produced	Pink colour produced	Artemether present
AL1, AL2, AL3, AL4, AL5, AL6 & ARTJ*	Yellow colour produced	Pink colour produced	Artemether present
No sample (negative control)	No yellow colour produced	No pink colour produced	Artemether absent

*Artemether injection; AL1–AL6 = Artemether-lumefantrine tablet brands.

Table 6. Test for authenticity of lumefantrine in artemether-lumefantrine tablets

Test sample	Observation (Test A)	Observation (Test B)	Inference
Pure lumefantrine powder (Positive control)	Orange precipitate produced within 5 min	Orange precipitate produced	A = Alkaloid (present) B = Lumefantrine (present)
AL1, AL2, AL3, AL4, AL5 & AL6	Orange precipitate produced within 5 min	Orange precipitate produced	A = Alkaloid (present) B = Lumefantrine (present)
No sample (Negative control)	No orange precipitate produced	No orange precipitate produced	A = No alkaloid B = Lumefantrine (absent)

AL1–AL6 = Artemether-lumefantrine tablet brands.

Table 7. Physical properties of artesunate (AT)/amodiaquine (AM) tablets

Sample code	Mean tablet mass (mg)	Crushing strength (N)	Disintegration time (sec)	Artesunate content (%)	Amodiaquine content (%)
AT1	302.1 ± 16.8	47.5 ± 39	107	49.4	–
AT2	281.5 ± 4	26.6 ± 6.5	155	58.6	–
AT3	346.5 ± 4.3	23 ± 6.4	202	177.7	–
AT4	207.4 ± 3	39.8 ± 6.4	590	85.7	–
AT5	354.9 ± 8.4	92.3 ± 9.7	163	79.5	–
AT6	603.1 ± 0.8	168.6 ± 0	441	60.7	–
AT7	296.3 ± 0.8	49.3 ± 12.4	12	42.0	–
AM1	507.7 ± 20.1	123.5 ± 34.9	540	–	115.0
AM2	308.4 ± 2.2	58.6 ± 17.6	20	–	148.9
AM3	592.5 ± 6.7	34.9 ± 6.2	60	–	142.8
AM4	519.4 ± 11.5	72.9 ± 11.1	60	–	113.2
AM5	481.7 ± 6.1	36.1 ± 19.6	90	–	141.9

Table 8. Physical properties of artemether-lumefantrine (AL) tablets and artemether injection

Sample code	Mean tablet mass (mg)	Crushing strength (N)	Disintegration time (sec)	Artemether content (%)	Lumefantrine content (%)
AL1	244.1 ± 1.7	112.4 ± 40	230	106.3	110.6
AL2	580 ± 2.6	109.6 ± 23.6	150	134.4	137.8
AL3	341.1 ± 6	81.7 ± 6.5	410	50.3	128.0
AL4	265.4 ± 4.8	46.7 ± 6.8	25	83.1	138.9
AL5	242.7 ± 1.1	48.2 ± 5.2	40	162.8	120.5
AL6	246 ± 2	71.9 ± 16	345	124.9	116.1
ARTJ*	–	–	–	79.0	–

*Artemether injection (80 mg/ml); AL1–AL6 = Artemether-lumefantrine tablet brands.

amount of artesunate (Table 7). Six (85.7%) of the artesunate tablet brands AT1, AT2, AT4, AT5, AT6 & AT7 were under dose (range: 42–85.7%) while brand AT3 was overdose (177.7%). All the amodiaquine tablet samples were overdose as they contained >107% of the labeled amount of amodiaquine (range: 113.2–148.9%). Artemether-lumefantrine tablet brands AL2, AL5 & AL6 contained an overdose of artemether (> 110.0%) whereas

AL3 & AL4 were underdose (Table 8). Only brand AL1 contained the appropriate amount of artemether (106.3%). Artemether injection (ARTJ) contained 79 % of artemether and was thus considered to be underdose. Apart from artemether-lumefantrine tablet brand AL1 which contained the stipulated amount of lumefantrine, the rest of the brands analysed contained far more than 110% of lumefantrine (range: 116.1–138.9%) and were thus considered to be overdose.

DISCUSSION

The quality of medicines can be assured and safeguarded in an environment having the requisite drug regulatory regime. In furtherance of this objective, all medicinal products, whether locally manufactured or imported, are required to be registered with the statutory drug regulatory agencies. In Ghana, the Food and Drugs Board is the statutory drug regulatory organization. The non-registration of most of the artemisinins investigated in the study by the statutory drug regulatory body is cause for serious concern. The source and quality of these unregistered antimalarial medicines cannot be guaranteed, thus putting the life of the patient at great risk.

The use of artemisinin monotherapy in malaria, especially in endemic countries has been strongly discouraged by the WHO. Instead, ACTs have been recommended as the first line medicines for the treatment of uncomplicated falciparum malaria in Ghana and other malaria endemic countries. Consequently, the WHO, through the World Health Assembly Resolution WHA60.18 of May 2007, committed member countries to stop the production and marketing of artemisinin monotherapies. The continuous availability of artesunate monotherapy tablets in licensed premises is, therefore, a major setback to the WHO antimalarial drug policy. This is because the WHO considers artemisinin monotherapy as substandard treatment even if the dosage of medication is appropriate[13]. The continuous usage of artesunate monotherapy in malaria will encourage the development of resistance to this life-saving medication with resultant treatment failures. Other studies have also reported the prevalence of artesunate monotherapy tablet brands in Ghana[8,9] and other African countries[13].

The qualitative tests employed to test the authenticity of the artemisinin-based antimalarials are simple field tests that are utilized to differentiate genuine medicines from fake or counterfeit medicines. These field tests can be employed to screen the artemisinins against counterfeit medication, particularly in resource poor countries in Africa and Southeast Asia which lack well-equipped laboratories for medicines testing. Such countries also tend to have weak drug regulatory systems. The results of the current study show that all the artemisinin-based antimalarials tested contained the specified active pharmaceutical ingredient(s) and none could thus be considered as fake or counterfeit medicine.

Most of the artemisinin-based tablets studied possessed the requisite physical attributes of mass uniformity, crushing strength and disintegration in aqueous medium. These properties provide preliminary information about the quality of the antimalarials. According to the International Pharmacopoeia artesunate tablets should contain not less than 90% and not more than 110% of the labeled amount of artesunate[20]. By this standard, all the artesunate brands tested did not comply with the specification and were of substandard quality. Five out of nine brands (55.6%) of artesunate tablets tested in Nigeria showed unacceptable quantity of active contents against the label claim[7]. Also, 64.7% of artesunate brands tested failed the WHO International Pharmacopoeia requirements for percentage content[8]. Amodiaquine hydrochloride tablets contain an amount of amodiaquine hydrochloride equivalent to not less than 93% and not more than 107% of the labeled amount of amodiaquine. All the amodiaquine samples were overdose as they contained more than 107% of the labeled amount of amodiaquine (range: 113.2–149%). Owing to the undesirable side effects of amodiaquine, an overdose of the medication will exacerbate the adverse effects and put the lives of patients in danger.

The International Pharmacopoeia specifies that artemether-lumefantrine tablets contain artemether and lumefantrine and they must contain 90–110% of the amounts of the two active ingredients stated on the label[20]. In the current study, five out of the six brands of artemether-lumefantrine tablet brands did not conform to the International Pharmacopoeia standards. A recent study showed that only two out of six brands of artemether-lumefantrine tablet brands purchased from different sources in Nigeria complied with the International Pharmacopoeia specifications[23]. Over dosing is as harmful as under dosing due to the various adverse effects that a patient may encounter. Under dosing may lead to treatment failure and may eventually result in mortality. Artemether injection is used as the first line treatment for complicated or severe falciparum malaria especially in cases where the patient is unable to take ACTs via the oral route. According to the International Pharmacopoeia, artemether injection contains not less than 95% and not more than 105% of the labeled amount of artemether[20]. The single artemether injection analysed (ARTJ) was found to contain 79.04% of artemether and was thus underdose and

substandard. A recent report in Ghana showed that one artemether injection (80 mg/ml) contained 70.5% of the label claim of artemether and was also substandard[9]. Since artemether injection is used in the treatment of complicated falciparum malaria, underdosing can lead to life threatening situations. All the brands of artemether-lumefantrine tablets analysed contained more than 110% of lumefantrine. An overdose of lumefantrine is undesirable and can result in potentially serious adverse effects like QT prolongation which can lead to arrhythmia and other cardiac complications.

Substandard antimalarials are caused by poor local regulation of the pharmaceutical industry, as well as poor pharmaceutical industry compliance with WHO good manufacturing practices (GMPs) in resource-poor countries, especially those in developing countries[24, 25]. The problem of substandard antimalarials can be mitigated through the strengthening of local drug regulatory agencies and improvement in medicine manufacturing processes[26]. This can be achieved through the setting up of well-resourced quality control laboratories, provision of requisite equipments, logistics, resources and training of personnel. Even though the study did not cover the whole of Ghana, the results nonetheless provides ample testimony of the problem of substandard artemisinin-based medicines in the country. This is because of similarity in demographic characteristics between the study area and other parts of the country, prevalence of illegal drug trade activities in other parts of the country and poor drug regulatory regime in the country as a whole.

CONCLUSION

Even though all the artemisinins tested contained the specified active pharmaceutical ingredient(s), most of the products did not contain the required amount of the drugs and are, therefore, of substandard quality. There is the need to strengthen drug regulatory agencies in Ghana and other resource-poor countries to undertake proper monitoring and evaluation of pharmaceuticals to stem this menace.

ACKNOWLEDGEMENT

The authors are grateful to the Chief Executive Officer of ASPEE Pharmaceuticals Company Limited, Ejisu, Ghana, for granting access to their Quality Control Laboratory for some analytical work.

REFERENCES

1. Attaran A, Barnes KI, Curtis C, d'Alessandro U, Fanello CI, Galinski MR, *et al*. WHO, the global fund and medical malpractice in malaria treatment. *Lancet* 2004; *363*(9404): 237–40.
2. *Counterfeit drugs – Guidelines for the development of measures to combat counterfeit drugs*. Geneva, Switzerland: Department of Essential Drugs and other Medicines, WHO; 1999: p. 1–62.
3. Kaur H, Goodman C, Thompson E, Thompson KA, Masanja I, Kachur SP, *et al*. A nationwide survey of the quality of antimalarials in retail outlets in Tanzania. *PLoS ONE* 3(10): e3403. doi: 10.1371/journal.pone.003403.
4. Gibson L. Drug regulators study global treaty to tackle counterfeit drugs. *Br Med J* 2004; *328:* 486.
5. Morris J, Stevens P. Counterfeit medicines in less developed countries – problems and solutions. London: International Policy Network 2006.
6. Dondorp AM, Newton PN, Mayxay M, van Damme W, Smithuis FM, Yeung S, *et al*. Fake antimalarials in Southeast Asia are a major impediment to malaria control: Multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health 2004; 9:* 1241–6.
7. Esimone CO, Okoye FBC, Onah BU, Nworu CS, Omeje EO. *In vitro* bioequivalence study of nine brands of artesunate tablets marketed in Nigeria. *J Vector Borne Dis* 2008; *45:* 60–5.
8. Ofori-Kwakye K, Asantewaa Y, Gaye O. Quality of artesunate tablets sold in pharmacies in Kumasi, Ghana. *Trop J Pharm Res* 2008; *7*(4): 1179–84.
9. Osei-Safo D, Harrison JJEK, Addae-Mensah I. Validation and application of quality assurance methods developed for artemisinin-based antimalarial drugs to assess the quality of a selection of such drugs distributed in Accra, Ghana. *African J Pharmaceutical Sci Pharma* 2010; *1*(1): 1–25.
10. Tipke M, Diallo S, Coulibaly B, Störzinger D, Hoppe-Tichy T, Sie A, *et al*. Substandard antimalarial drugs in Burkina Faso. *Malar J* 2008; *7:* 95.
11. Atemnkeng MA, De Cock K, Plaizier-Vercammen J. Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo. *Trop Med Int Health* 2007; *12*(1): 68–74.
12. Newton PN, McGready R, Fernández FM, Green MD, Sunjio M, Bruneton C, *et al*. Manslaughter by fake artesunate in Asia: Will Africa be next? *PLoS Med* 2006; *3*(6): e197. doi: 10.1371/journal.pmed.0030197.
13. Bate R, Coticelli P, Tren R, Attaran A. Antimalarial drug quality in the most severely malarious parts of Africa – a six country study. *PLoS ONE* 2008; *3*(5): e2132. doi: 10.1371/journal.pone.002132.
14. Hall KA, Newton PN, Green MD, De Veij M, Vandenabeele P, Pizzanelli D, *et al*. Characterisation of counterfeit artesunate antimalarial tablets from South East Asia. *Am J Trop Med Hyg* 2006; *75*(5): 804–11.
15. Newton PN, Dondorp A, Green M, Mayxay M, White NJ. Counterfeit artesunate antimalarials in Southeast Asia. *Lancet* 2003; *362*(9378): 169.
16. Rozendaal J. Fake antimalaria drugs in Cambodia. *Lancet* 2001; *357*(9259): 890.
17. Green MD, Mount DL, Wirtz RA, White NJ. A colorimetric field method to assess the authenticity of drugs sold as the antimalarial artesunate. *J Pharm Biomed Anal* 2000; *24:* 65–70.
18. Ioset JR, Kaur H. Simple field assays to check quality of current artemisinin-based antimalarial combination formulations. *PLoS ONE* 2009; *4*(9): e7270. doi: 10.1371/journal.pone.0007270.
19. United States Pharmacopoeia and National Formulary. USP29-NF24 2010; p. 155.

20. *International Pharmacopoeia. Monographs for antimalarial drugs*, v. 5. III edn. Geneva: World Health Organization 2003; p. 185–234.
21. Shrivastava A, Nagori BP, Saini P, Issarani R, Gaur SS. New simple and economical spectrophotometric method for estimation of artemether in pharmaceutical dosage forms. *Asian J Res Chem* 2008; *1*(1): 19–21.
22. da Costa César I, Nogueira FH, Pianetti GA. Comparison of HPLC, UV spectrophotometry and potentiometric titration methods for the determination of lumefantrine in pharmaceutical products. *J Pharm Biomed Anal* 2008; *48*(1): 223–6.
23. Awofisayo SO, Willie E, Umoh E. Quality control evaluation of multi-source artemether-lumefantrine tablets prescribed for uncomplicated multi-drug resistant malaria. *Indian J Novel Drug Delivery* 2010; *2*(4): 153–7.
24. Caudron JM, Ford N, Henkens M, Macé C, Kiddle-Monroe R, Pinel J. Substandard medicines in resource-poor settings: A problem that can no longer be ignored. *Trop Med Int Health* 2008; *13*(8): 1062–72.
25. Senior K. Global health-care implications of substandard medicines. *Lancet Infect Dis* 2008; *8*(11): 666.
26. Newton PN, Green MD, Fernández FM. Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol Sci* 2010; *31*(3): 99–101.

Correspondence to: Prof K. Ofori-Kwakye, Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.
E-mail: koforikwakye@yahoo.com; kokwakye.pharm@knust.edu.gh

Received: 1 March 2012 *Accepted in revised form:* 18 July 2012