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Quality of chloroquine tablets available in Africa

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Malaria is the biggest killer of African children, yet it is cheaply preventable and curable with insecticides spraying, impregnated bednets and effective drugs. This study aimed to evaluate the quality of Chloroquine (CQ) tablets available in selected African countries. Twenty-six samples of antimalarial CQ tablet of 100, 150 and 250 mg were collected from 12 African countries and evaluated for their quality in the Drugs Quality Control Laboratory of Rabat, Morocco. The identification and dosage of active pharmaceutical ingredients in the tablets, dissolution rate, hardness and the friability of CQ tablets were performed according to the United States Pharmacopeia (USP) and European Pharmacopoeia (Eur.Ph.) recommended methods. The results showed that 7.7% of the sampled CQ tablets available in Burkina Faso were of low quality. Failure in dissolution profile was found in 50% of CQ tablets sampled from Benin, Burkina Faso, Comoros Union, Mali and Senegal. The findings showed poor quality of CQ tablets available in the African market. This problem may affect the efforts to control malaria in Africa. Efficient regulatory systems of drugs quality control should be implemented.

INTRODUCTION

In spite of the high burden of malaria and the focus of its control in Africa, malaria remains one of the most important public health problem in the continent. WHO has estimated that about 85% and 89% of the 243 million cases of malaria and 863 000 deaths, respectively, reported worldwide were in Africa (WHO, 2009). Antimalarial drug resistance is now recognized to be the greatest problem facing malaria control efforts (Dondorp *et al.*, 2009). Inadequate treatment (e.g. sub-therapeutic dosage, sub-standard drug) of high biomass infections will not kill mutant parasites and is the major selective pressure for resistance (Falade *et al.*, 2008). In order to delay or even overcome the emerging of resistance, the control of malaria chemotherapy requires reducing the overall drug pressure throughout more selective use of qualified drugs and improving the ways the drugs are used and sold in the markets. However, one of the most critical challenges to the chemotherapy of malaria in developing countries is the wide scale availability of fake and substandard drug products (Ten, 2003). Quality control is an important process in the pharmaceutical industry and marketing of safe drugs with consistent and predictable therapeutically active formulations (Levi *et al.*, 1964).

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Although the current antimalarial drug policies in many African countries recommend either artemether–lumefantrine or a combination of Artesunate and Amodiaquine instead of Chloroquine (CQ) and sulfadoxine–pyrimethamine but, in practice, CQ is still extensively used even in areas with established resistance (WHO, 2008). This could be due to that CQ is the cheapest and perhaps the safest antimalarial drugs in all populations of patients. Therefore, this study aimed to assess the quality of CQ tablets 100, 150 and 250 mg available at different levels of the distribution chain in 12 African countries, namely, Benin, Burkina Faso, Cameroon, Ivory Coast, Gabon, Ghana, Union of the Comoros, Mali, Morocco, Niger, Senegal and Chad.

MATERIALS AND METHODS

Study Design and Study Area

This pilot study was conducted in 12 selected African countries where CQ remains the most frequently used drug to treat malaria. These countries have adopted Artemisinin-based combination therapy (ACT) recommended by the WHO and five of them, namely, Burkina Faso, Gabon, Union of the Comoros, Niger, Senegal, provide it free for malaria patients. In the other six countries, patients must pay to get these drugs which considered being expensive (WHO, 2008).

Samples Collection

Twenty-six samples of different lots and batches numbers (50–100 tablets of each sample) of marketed antimalarial CQ salt tablets of 100, 150 and 250 mg were collected from the countries involved in this study. The samples (different manufacturers) were collected randomly at various levels of the drug distribution chain, such as pharmacies, stores, suppliers, universities medical centres and peddlers at the capitals of the countries involved in this study. The number of products collected from each country was based on the available products. Serially coded labels were used to collect information on drugs during sample collection. Information on the country, date of collection, location of sample collection point, facility name and type, brand name, strength, date of manufacture and expiry and any observation on storage were collected. The samples were then sent to be processed and evaluated in the Drugs Quality Control Laboratory of Rabat, Morocco, according to the procedures recommended by the United States Pharmacopeia and European Pharmacopoeias (USP, 2006; Eur.Ph., 2008). As per USP monograph (USP, 2006), weight uniformity, tablet thickness and diameter, friability and hardness, active pharmaceutical ingredient and dissolution profiles should be assessed to determine whether or not the drug batch has met all acceptance criteria before the batch is declared to be passed or failed the quality evaluation.

Identification and Determination of Doses of CQ Tablets

The contents of CQ tablets were determined by a UV spectrophotometer according to the USP method (USP, 2006). Twenty tablets were weighted and pulverized to a fine powder. Tablets powder equivalent to 800 mg of CQ salt was extracted and transferred into a 200 ml volumetric flask. Then, 100 ml of water were added and shaken by a separator funnel for about 20 minutes. After that, the mixture was filtered and the first 50 ml of the filtrate were discarded; 50 ml of the clear filtrate were transferred to a 250 ml volumetric flask, 5 ml of 6 N ammonium hydroxide were added and shaken, and the liberated CQ was extracted with 25 ml of chloroform. The combined chloroform extracts were evaporated using a steam bath to about 10 ml, and then 20 ml of 0.1 M HCl were added. Evaporation process was continued until the odour of chloroform is not longer perceptible. Transfer the contents into a 200 ml volumetric flask and wash the evaporating vessel with 0.1 M

HCl. Then, the washings were transferred into a volumetric flask, and 10 ml of diluted HCl were added, and mixed. These solutions were diluted into a volume of 25 ml with diluted HCl to obtain an estimated concentration of 10 μg/ml. An accurately weighted quantity of USP CQP RS was dissolved in the diluted HCl and the absorbance of the solution was measured by a spectrophotometer (PerkinElmer, Waltham, MA, USA) at a wavelength of 343 nm.

Dissolution Profiles of CQ Tablets

Dissolution test is performed to obtain information about the possible differences in the bioavailability (the amount of active ingredient released and available for absorption) of the sampled CQ tablets. According to the USP monograph, tolerances for CQ tablets not less than 80% of the labelled amount are dissolved in 45 minutes. The dissolution rate determination on conventional CQ tablets was carried out according to the specific methods described in the USP monograph using the recommended Paddle method (USP, Apparatus 2), at a stirring rate of 100 rev/min for 45 minutes (USP, 2006). The dissolution medium was 900 ml of distilled water at $37 \pm 0.5^{\circ}$C. The amount of CQ dissolved in 45 minutes was determined by a UV spectrophotometer at wavelength of 343 nm in filtered portions of the solution under test in comparison with a standard solution of USP CQ phosphate and was expressed as a percentage of the label claim.

Hardness and Friability Test of QC Tablets

This is to determine the physical strength of tablets upon exposure to mechanical shock, attrition and weight loss. The test was performed using a hardness tester on 10 tablets from each brand. Ten tablets from each brand were also weighted and put into the friabilitor. Tablets were rotated at 25 rev/min, and then the friability percentage was calculated for each batch (Eur.Ph., 2008).

RESULTS

Twenty six samples were collected from licensed pharmacies, wholesaler, sidewalk pharmacies and universities' medical centres. The basic information of the collected drugs is shown in Table 1. The tablets are produced by different domestic and foreign manufacturers; only countries of origin were given in the table.

Dosage of active pharmaceutical ingredient and dissolution test of the sampled CQ tablets were measured and the results are shown in Table 2. From the table, 7.7% of the sampled CQ tablets showed low dosage of active component which did not meet the acceptance criteria for CQ tablet in the USP: 93%–107% of the stated amount per unit. These were two products (products 5 and 6) sampled from Burkina Faso and showed the lowest percentage of active pharmaceutical ingredients (API%): 81.88% and 60.50%, respectively. Regarding the dissolution test, 50% (13/26) of the samples from Benin, Burkina Faso, Comoros Union, Mali and Senegal showed failure in dissolution test profile and were not in conformity with USP standards. Failure in release of CQ from tablets matrix was reported and 50% of the products showed dissolution rates lower than the USP recommended rate ($\geqslant$80% of the label claim), and product 6 showed the lowest dissolution rate (49.94%). This failure was reported at different levels of distribution chain.

The hardness and friability of the tablets were assessed and the results are shown in Table 3. Differences in tablets hardness of some batches are due to the differences in the process of tablets manufacturing mainly the compression force. In general, the tablets hardness was neither low to become friable nor high to affect the disintegration and dissolution of products. The highest and lowest values of hardness were

TABLE 1. *Basic information of the sampled Choloroquine tablets*

Countries	Product no.	Manufacturers	CQ salt	Manufactures Countries	Dose (mg)	Packaging	Tablets quantity	Collection
Benin	Product 1	Labo Creat	CQP	France	100	Blister 10	80	Pharmacy
	Product 2	Pharma	CQP	Benin	100	Bottles 30		Pharmacy
		Quik-SA,					90	
Burkina Faso	Product 3	Phyto-Riker (GIHOC)	CQP	Ghana	100	Blister 10		Wholesaler
		Pharmaceuticals					70	
	Product 4	Smithkline Beecham	CQP	India	100	Blister 10		Wholesaler
		Pharmaceuticals					100	
	Product 5	Troge	CQP	Germany	100	Bottles 70	70	Pharmacy
	Product 6	Lafran	CQP	France	100	Bottles 70	70	Pharmacy
	Product 7	Mission	CQP	Denmark	100	Bottles 70		Pharmacy
		Pharma					70	
	Product 8	Smithkline	CQP	England	100	Bottles 70		Pharmacy
		Beecham					70	
	Product 9	Clarion	CQP	England	150	Blister 10		Sidewalk
							60	pharmacy
Cameroon	Product 10	Aventis	CQS	Senegal	100	Blister 10	100	Pharmacy
	Product 11	Strides	CQP	India	100	Blister 10		wholesaler
		Arcolab Ltd					80	
	Product 12	Strides	CQP	India	100	Blister 10		Pharmacy
		Arcolab Ltd					70	
Ivory Coast	Product 13	Cipharm	CQP	Ivory Coast	100	Blister 10		Pharmacy
							80	
Gabon	Product 14	MIB	CQP	Maurice	100	Blister 10		National
		Goodlans		Island				Pharmaceutical
							80	Office (NPO)
	Product 15	SSG	CQP	Gabon	100	Blister 10		NPO
		Pharmaceutical					70	
Ghana	Product 16	Erenst	CQP	Ghana	250	Blister 10		Pharmacy
		Chemistis						
		Limited					70	
Comoros	Product 17	PNAC	CQP	Comoros	100	Bottles 80		PNAC
							80	Regional
Mali	Product 18	UMPP	CQP	Mali	100	Blister 10	80	Pharmacy
	Product 19	PRG	CQP	Ghana	100	Blister 10	80	Pharmacy
	Product 20	PRG	CQP	Ghana	100	Blister 10	80	Pharmacy
Morocco	Product 21	Aventis	CQS	Morocco	100	Blister 10	70	Industries
Niger	Product 22	Pharma	CQP	Denmark	100	Blister 10		ONPPC
		Danica					60	
	Product 23	GIHOC	CQP	Ghana	100	Blister 10		Pharmacies
		Pharmaceuticals					100	
	Product 24	Pharma	CQP	Niger	150	Bottles 50		Sidewalk
		Danica					50	pharmacy
Senegal	Product 25	Aventis	CQS	Senegal	100	Blister 10	70	Pharmacy
Chad	Product 26	Aventis	CQS	Chad	100	Blister 10		Sidewalk
							50	pharmacy

CQP, Chloroquine phosphate; CQS, Chloroquine sulphate.

found in product 22 (10.0) and product 14 (2.1), respectively. On the other hand, Table 5 showed that the friability results for the tablets were acceptable and meet the friability of CQ tablet recommended by Eur.Ph. ($\leqslant 1\%$).

DISCUSSION

Malaria is still endemic in 109 countries, and 45 of them are in Africa with about 90% of all malaria deaths in the world (WHO, 2009). In Africa, antimalarial drugs are widely available outside the public health services, from shops and private practitioners and about two-thirds of all malaria cases are initially treated by private providers. However, the quality of these drugs provided by informal private sector is suspect. Moreover, recent household surveys in few African countries where ACT is provided free of charge for malaria patients found that only 3% of children with fever were treated with ACT, while 38% of them were given any antimalarial drug (mainly CQ) from any source (WHO, 2008). This indicates that the supply of alternative drugs (including ACT) was still inadequate to compensate for progressive CQ disuse.

The quality control assessment was done in this study to evaluate the quality of antimalarial drugs in the market of 12 African countries. Findings of the present study showed that two products of CQ tablets sampled from Burkina Faso (collected from two different pharmacies) were found to be of low quality, and 50% failure in dissolution test profile of the products from Benin, Burkina Faso, Comoros Union, Mali and Senegal were not consisted with USP standards. Moreover, the high RSD% values observed in dissolution tests for tablets from these countries indicate a large

TABLE 2. *Dosage of active ingredient and dissolution test of the sampled CQ tablets*

		Active pharmaceutical ingredient		Dissolution test	
Countries	Product no.	API%	RSD%	Dissolution rate (%)	RSD%
Benin	Product 1	98.54	0.74	84.29	2.50
	Product 2	93.16	1.86	56.60	9.10
Burkina Faso	Product 3	96.26	2.72	78.04	4.09
	Product 4	96.76	0.76	84.12	1.76
	Product 5	81.88	2.20	75.69	2.63
	Product 6	60.50	0.44	49.94	1.20
	Product 7	94.73	2.52	68.71	1.98
	Product 8	96.65	3.28	68.66	2.30
	Product 9	150.81	0.71	86.11	0.93
Cameroon	Product 10	97.05	1.04	71.83	5.31
	Product 11	95.35	0.74	86.48	2.57
	Product 12	94.27	1.02	77.32	1.97
Ivory Coast	Product 13	99.48	0.49	82.74	2.69
Gabon	Product 14	94.24	0.45	83.23	3.97
	Product 15	97.72	1.45	84.04	2.90
Ghana	Product 16	249.44	1.84	87.45	1.55
Comoros	Product 17	102.50	3.90	73.42	1.92
Mali	Product 18	94.86	1.49	78.34	3.62
	Product 19	97.45	2.27	71.41	2.18
	Product 20	93.97	0.64	66.17	1.85
Morocco	Product 21	97.67	0.83	80.65	2.92
Niger	Product 22	95.38	1.06	80.87	1.08
	Product 23	100.68	1.17	84.81	3.01
	Product 24	151.72	2.39	88.02	2.04
Senegal	Product 25	97.36	1.19	78.49	9.00
Chad	Product 26	97.00	1.18	83.80	2.81

RSD, relative standard deviation.

variability in the production process. This could be attributed to the effect of formulation excipients and the manufacturing processes. Furthermore, poor quality of the CQ tablets reported by the present study may indicate the absence of regulatory systems of drugs quality control in these countries, and this may contribute to the drug resistance in these countries especially with the common practice of self-medication. However, not all drugs are produced under good manufacturing practice and even well-established pharmaceutical companies which follow the recommended standards might produce drugs of poor quality which may have negative effects on the therapeutic action (White, 2004).

In comparison with previous studies, there are substandard antimalarial products circulating within the drug distribution chains in Yemen, which will have serious implications on the reduced therapeutic effectiveness and on the development of drug resistance (Abdo-Rabbo *et al.*, 2005). This appears to be due to non-compliance with the good manufacturing practices guidelines by manufacturers in the production of the antimalarial drugs. Previous studies in Southeast Nigeria and Sudan revealed that the poor-quality drugs are highly distributed and circulating intensively in the market (Alfadl *et al.*, 2006; Onwujekwe *et al.*, 2009). However, availability of substandard drugs is the most important challenge to the chemotherapy of malaria and other infectious diseases in the developing communities (Ofonaike *et al.*, 2007).

Evaluation of antimalarial quality in Africa by WHO revealed that significant problems

TABLE 3. *Hardness and friability of the sampled CQ tablets*

		Hardness		
Countries	Product no.	Mean ± SD (kg)	RSD%	Friability (%)
Benin	Product 1	5.0 ± 0.7	13.6	0.15
	Product 2	5.5 ± 0.5	9.2	0.28
Burkina Faso	Product 3	3.1 ± 0.5	16.6	0.34
	Product 4	3.3 ± 0.4	13.4	0.04
	Product 5	5.0 ± 0.5	10.6	0.19
	Product 6	4.0 ± 0.6	14.7	0.15
	Product 7	3.3 ± 0.9	28.4	0.30
	Product 8	3.8 ± 1.2	31.0	0.03
	Product 9	7.6 ± 1.4	17.8	0.30
Cameroon	Product 10	4.3 ± 0.5	11.1	0.15
	Product 11	5.0 ± 0.8	15.8	0.04
	Product 12	4.8 ± 0.8	14.1	0.02
Ivory Coast	Product 13	7.7 ± 1.4	18.5	0.17
Gabon	Product 14	2.1 ± 0.6	27.5	0.28
	Product 15	3.1 ± 0.9	29.3	0.36
Ghana	Product 16	5.2 ± 1.3	24.7	0.24
Comoros	Product 17	3.5 ± 0.5	13.5	0.06
Mali	Product 18	3.8 ± 0.7	17.3	0.50
	Product 19	3.6 ± 0.5	15.0	0.32
	Product 20	2.9 ± 0.4	14.1	0.28
Morocco	Product 21	7.7 ± 1.2	15.0	0.21
Niger	Product 22	10.0 ± 1.7	17.0	0.00
	Product 23	3.2 ± 0.8	24.2	0.31
	Product 24	2.9 ± 0.5	15.5	0.57
Senegal	Product 25	4.9 ± 1.0	20.1	0.43
Chad	Product 26	4.0 ± 0.4	10.3	0.37

RSD%, relative standard deviation.

of substandard products exist within the drug distribution chains. A previous study concluded that reasons for the wide variations in the content of CQ tablet may include poor manufacturing practice (low-quality drugs), long and unfavourable condition of distribution chains, or just poor storage conditions (Ogwal-Okeng *et al.*, 2003). Therefore, control programmes should establish efficient systems to monitor antimalarials drug efficacy especially in developing countries where the problems of quality failure predominantly occur due to lacking of effective drug regulatory agencies and proper drug quality testing laboratories (WHO, 2001; Maponga and Ondari, 2003). A drug quality monitoring system would encourage the manufacturers to improve good manufacturing practice and help to identify counterfeit or poor-quality pharmaceuticals and this will help to combat malaria and other diseases (Green, 2006).

In conclusion, this study showed poor quality of QC tablets sampled from Africa and this could be attributed to the absences of efficient regulatory systems. Poor quality of antimalarial drugs may affect the efforts to control malaria and providing high-quality antimalarials drugs will significantly reduce malaria related deaths in Africa. Although CQ treatment failures against malaria are usually due to drug resistance, low compliance or the use of CQ preparations of poor quality could also contribute to this failure.

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