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Quality of Antimalarial Drugs in Malaria Endemic Municipalities of Pangasinan, Philippines

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Abstract

Malaria is a major public health problem in the South-East Asia (SEA) including Philippines. In the Philippines, Seventy-four provinces are considered malaria endemic with around 11 million Filipinos at risk of malaria. Previously, no study looked at the quality of antimalarial drugs circulating in these malaria endemic municipalities including those of Pangasinan. The present study determined the quality of available anti-malarial drugs in the malaria endemic municipalities of Pangasinan.The quality of the samples of available antimalarial drugs was determined using disintegration and in-vitro dissolution tests, and also based on their physico-chemical characteristics according to United States Pharmacopoeia (USP). All anti-malarial drugs from the Government Units of the Municipal Health Offices of selected municipalities in Pangasinan as well as the commercially available OTC drugs passed their physico-chemical evaluations. They had disintegration times within the specified limits prescribed by United States Pharmacopeia (USP). All the samples of Artemether Lumefantrine combination tablets passed dissolution tests. However, they had mean dissolution of 78.97 % (range 75.84 to 81.9) that is marginal. Only fifty percent (50%) of all the Chloroquine phosphate samples passed the dissolution tests. Artemether Lumefantrine combination and Chloroquine phosphate samples in this study had good disintegration times but showed poor dissolution tests results. The effects of these poor *in vitro* dissolution tests results on their *in vivo* metabolism and bioavailability, as well as their drug – drug interactions need further investigations.

Keywords: Malaria, drugs, quality, Philippines

INTRODUCTION

Malaria is a major public health problem in the South-East Asia (SEA) Region. Out of 11 countries of the Region, 10 countries are malaria endemic. About 40% of the global population at risk of malaria resides in SEA Region and accounts for 15% of the global reported confirmed cases and around 2.7% of the global mortality due to malaria. During 2000-2009, in SEA Region, malaria incidence was between the range 2.16 -2.83 millions and malaria deaths between 3188 - 6978 (Eduardo Gonzales, 2010). The *Plasmodium falciparum* proportion lies between 44 – 60%, slide

positivity rate. The increasing proportion of *P. falciparum* in the Region is alarming and needs special attention to deal with it (Lansang, 1996).

Although the Philippines does not contribute significantly to the global mortality from malaria, the disease is a major cause of healthy days of life lost (HDLL) in the endemic areas of the country. In the Philippines, out of 77 provinces, 74 are considered endemic, with around I1 million Filipinos at risk of malaria (Lansang, 1996). Of residents in these endemic areas, around 7% reside in areas stratified by the Department of Health's Malaria Control Service as Malarious "A" areas (mostly mobile population in forest and forest-fringe areas, with >2 % parasite rate); 25 % are in Malarious "B" areas (mostly stable population in foothills and plains with > 2 % parasite rate); while around 68 % are in Malaria Epidemic -Prone Areas like the province of Pangasinan.

Malaria endemicity in the Philippines is now generally characterized as moderate to low. Within such hypo-endemic areas, however, are clusters of “hot spots” where high transmissions still exist. Areas where these pockets of high endemicity persist are characterized as: rural, hill/mountainous, associated with streams, remote and very hard to reach, frontier and regions.

Malaria is the eighth leading cause of morbidity in Philippines. Data for over ten years show that more than 90% of malaria cases nationwide are found in 25 of the 74 endemic provinces (Roll Back Malaria, 2010). Within such hypo-endemic areas, however, are clusters of “hot spots” where high transmissions still exist. Areas where these pockets of high endemicity persist are characterized as: rural, hill/mountainous associated with streams, remote and very hard to reach frontier and regions (Geographical Distribution of Malaria, Philippines, 2010).

In Pangasinan Philippines, over the years a lot has been done to eradicate malaria. Malaria recorded in 2011 in the province of Pangasinan was from four towns Infanta, Mabini, Aguilar and Mangatarem (unpublished data, Pangasinan Provincial Health Office). These towns are on the foot of a hill, with streams and classified as rural.

One of the possible reasons for continued prevalence and incidence of malaria is the syndication of antimalarials. Antimalarial medications are designed to prevent or cure malaria. Antimalarial drug resistance has been a serious problem lately (World Health Organization (WHO), 1993). Drug resistant parasites are often the cause of malaria treatment failure (Caudron et al. 2008).

Drug quality should be considered at all stages of the drug management cycle. Poor quality drugs decrease efficacy, affect the reputation of the drug and under-mine the treatment policy (Roll Back Malaria, 2011). Safety, quality, and efficacy of medicines are the three most important criteria used by governments to regulate pharmaceuticals. Quality of drugs is especially important and is one of the earliest to come under government scrutiny. As a result, it is therefore of vital importance that antimalarial drugs administered are genuine and of high quality. Poor quality of drugs can be divided into two categories: counterfeit and substandard. Counterfeit drugs are deliberately and fraudulently mislabeled with respect to identity, source, or both. Counterfeit can apply to both branded and generic products and could include products with the correct ingredients or with the wrong ingredients, without active ingredient, with insufficient active ingredient, or with fake packaging. Substandard drugs are genuine drug products that upon laboratory testing do not meet the quality specifications claimed by their manufacturers. This may reflect substandard manufacturing technology, or inappropriate storage and transportation. Many developing countries do not have technical, financial or human resources required for inspecting and policing the drug supply. WHO has estimated that about 25% of the medicines consumed in developing countries are counterfeit (Antimalarial medication, 2011).

Presently, there is no study of the quality of antimalarial drugs in the malaria endemic areas of the Philippines. In this study, we used drug disintegration and dissolution tests, according to British Pharmacopoeia (British Pharmacopoeia, 2007) and United States Pharmacopoeia USP, 2007), respectively including physico-chemical characteristics as criteria to determine the quality of antimalarial drugs used for malaria treatment in the malaria endemic Municipalities of Pangasinan in Philippines.

MATERIALS AND METHODS

Drug sampling and collection

This study adopted the same methods used by WHO to assess the quality of antimalarial drugs in malaria endemic countries (Kaur et al 2010). Therefore, samples were collected at various levels of drug distribution in both public and private sectors. Three community pharmacies/drug stores in Infanta and Mabini, four drug stores in Aguilar and five drug stores in Mangatarem provided the Chloroquine samples. Artemether and Lumefantrine combination tablets subsidized by the government were obtained from the Rural Health Units (RHU) of the municipalities. The drugs samples collected from all the levels were 18 tablets of Artemether Lumefantrine and 32 tablets of Chloroquine phosphate. A total of fifty (50) tablets were collected, coded and prepared for analysis.

Physico-chemical characteristics

This study was approved by Virgen Milagrosa University, San Carlos City, Pangasinan, Philippines and the results compared with the Philippines Food and Drug Administration standard and USP specifications. Experiments were conducted at the College of Pharmacy laboratory, Virgen Milagrosa University.
The physico-chemical characteristics of both Artemether Lumefantrine combination and Chloroquine phosphate samples were done according to USP. Six tablets from each group, selected randomly were visually checked for their appearances, uniformity in the colour of the tablets and were weighed individually using a digital balance from which means were calculated and percentages determined.

Disintegration Test

The disintegration time of tablets was determined as previously described in the British Pharmacopoeia (British Pharmacopoeia, 2007). Briefly, six tablets were placed in each compartment of the disintegration apparatus (TD-20S Campbell Electronics, Thermonik, Mumbai, India) with double distilled water at 37^{o}C as medium. The tablets were considered to have passed the test after all 6 tablets had passed through the mesh of the disintegration apparatus within 15 -30 minutes.

Dissolution Test

The dissolution test for the present study used the paddle method. Dissolution tests were performed using USP Apparatus 2 paddle type (Dissolution Tester DT-6, Hsiangtai Machinery Industry Co, LTD. Taiwan, ROC) at a paddle speed of 75rpm. The dissolution medium used was 500ml Hydrochloric acid 0.01 USP. Each test comprised of 6 tablets in every round of dissolution test. Each tablet was dropped in a refraction flask in every round of dissolution test. The dissolution time based on USP standard was 30 minutes. A 5ml sample aliquot was then withdrawn at 10 minutes, 20 minutes and 30 minutes using micropipettes and immediately replace with equal volume of fresh medium at the same temperature (37^{0} C) to maintain constant total volume during the test. All samples were filtered through membrane filters and these were subjected to a UV spectrophotometer at 343nm to determine the percentage of drug that has dissolved.

Data Analysis

The data gathered were input into a computer and subsequently analyzed. Thereafter, data obtained were compared to the various USP standard values.

RESULTS

Quality of the antimalarial drugs as to Physico-chemical characteristics

All tablets including Artemether Lumefantrine combination and Chloroquine phosphate from various towns and municipal RHU showed satisfactory evaluation of their packaging, colours and the tablets are all free from mottling or mark with spots or blotches of different shades or colors.
Furthermore, all of the tablets passed in terms of tablets weight variation. The weights of the tablets are not lower or greater than 7.5% of the average tablets weights which are 226.79 mg and 263.75mg as stipulated by USP-National Formulary for Artemether Lumefantrine combination. Chloroquine phosphate tablets also passed in terms of weight variation from 503.23 mg to 556.21 mg, within 5% of the average weight of the tablets (USP-NF).

Disintegration Tests

As stated in table 1, all of the tablets (100%) of the Artemether and Lumefantrine combination, and Chloroquine phosphate had disintegration times that are within the specified limits prescribed by the USP that a drug should disintegrate within 15 - 30 minutes.

Table 1. Disintegration of available anti-malarial drugs in malaria endemic municipalities of Pangasinan Philippines

Samples	Tablet No	Disintegration Time (min.)	SD Time	Interpretation	Percentage
AL	1	2.41	Within 30mins	PASSED	100%
	2	2.40		PASSED	
	3	2.38		PASSED	
	4	2.40		PASSED	
	5	2.40		PASSED	
	6	2.41		PASSED	
MDS-CQ	1	6.05	Within 30mins	PASSED	100%
	2	6.06		PASSED	
	3	6.04		PASSED	
	4	5.03		PASSED	
	5	7.59		PASSED	
	6	6.02		PASSED	
ADS-CQ	1	5.01	Within 30mins	PASSED	100%
	2	5.01		PASSED	
	3	5.05		PASSED	
	4	5.01		PASSED	
	5	5.01		PASSED	
	6	5.01		PASSED	

Disintegration time of available anti-malarial drugs in malaria endemic municipalities of Pangasinan Philippines. All anti-malarial drugs samples AL, MDS-CQ and ADS-CQ had their disintegration times between 2-8 minutes of the standard 30 minutes as stated in British Pharmacopoeia (British Pharmacopoeia, 2007). Samples n==6 for each drug. AL = Artemetar lumefanterin combination, MDS-CQ = Chloroquin tablets from MDS, ADS-CQ = Chloroquin tablets from ADS, SD Time = Standard disintegration time.

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Dissolution Tests

As shown in table 2, all of the six (6) or 100% of tablet samples of the generic drug Artemether Lumefantrine combination passed the dissolution test within 30 minutes at mean dissolution values of 78.97 % (range 75.84 to 81.9). These are marginally higher than the required 75% release of the drug as prescribed by USP-NF.
However, only 50% tablets of Chloroquine Phosphate coded as MDS-CQ passed dissolution test wherein the percentage of drug released from the tablet were 90.24%(t1), 81.33% (t2) and 95% (t3). The other 50% failed with percentages of drug released far lower than 75% as 64% (t4), 44.86% (t5), and 49.32% (t6). Similarly, only 50% of Chloroquine Phosphate coded as ADS-CQ passed the disintegration test with percentages of drug released as 97.87% (t1), 87.83% (t2), 91.54 (t3) and the rest failed with the percentages of drug released as 62.49% (t4), 57.61% (t5) and 52.09% (t6) also lower than the prescribed USP standard of 75% release.

Discussion

To the best of our knowledge, the present study is the first to look at the quality of antimalarial drugs in use in the Philippines malaria endemic municipalities using WHO adopted methods of assessing drug quality. Both Artemether Lumefantrine combination and Chloroquine Phosphate had good results as to their physico-chemical characteristics and disintegration tests time within the specified limits prescribed by the USP. Appearances of the packs checked visually were authentic and conform to USP specifications. Uniformity in color of the tablets is an important parameter, which showed that the tablets are free from mottling or marks with spots or blotches of different shades or colors.

The time of disintegration is a measure of the quality. This means that both Artemether and Lumefantrine combination and Chloroquine Phosphate are within the specified quality in terms of their possibility to break when taken by the patients. However, the dissolution test results of the Artemether and Lumefantrine combination was only marginal while those of Chloroquine Phosphate even from different manufactures had just fifty percent (50%) that passed the

Table 2. Dissolution time of anti-malarial drugs available in municipalities of Pangasinan Philippines

Sample	Tablet No	Dissolution Profile (%) in 30 minutes	Standard (%)	Interpretation	Percentage
AL	1	78.0	75	PASSED	100%
	2	78.17		PASSED	
	3	78.0		PASSED	
	4	75.84		PASSED	
	5	81.9		PASSED	
	6	81.9		PASSED	
MDS-CQ	1	90.24	75	PASSED	50%
	2	81.33		PASSED	
	3	64.0		FAILED	
	4	44.86		FAILED	
	5	96.0		PASSED	
	6	49.32		FAILED	
ADS-CQ	1	97.87	75	PASSED	50%
	2	62.49		FAILED	
	3	57.61		FAILED	
	4	52.09		FAILED	
	5	87.83		PASSED	
	6	91.54		PASSED	

Dissolution time of available anti-malarial drugs in in malaria endemic municipalities of Pangasinan Philippines. All samples AL passed their dissolution test and all had dissolution of 78.0% - 81.9% within the stipulated 30 minutes dissolution time for 75% of samples. Samples from MDS-CQ and ADS-CQ had only 50% passed the dissolution each. Samples n==6 for each drug. AL = Artemetar lumefanterin combination, MDS-CQ = Chloroquin tablets from MDS, ADS-CQ = Chloroquin tablets from ADS

dissolution tests. Poor dissolution tests may affect drug absorption and lead to decreased bioavailability. This may also lead to poor drug –drug interactions.

Treatment failure, ascribed to drug resistance, may also be due to low quality drugs leading to poor drug absorption and decreased bioavailability, yet in most countries the quality of antimalarials are rarely independently verified, and the local capacity for independent drug quality assurance is worst where the disease burden is highest. Although malaria-endemic countries carry out drug resistance monitoring in accordance with the WHO protocol lately, there are no data linking these treatment failures to drug resistance with drug quality (Maponga and Ondari, 2003). Good dissolution test results gives assurance that the drug will be released satisfactorily *in vivo* and should lead to a good bioavailability (Odunfa et.al, 2009). Having good bioavailability will then lead to proper treatment of patients but poor bioavailability (as suggested would be the case in this study) will lead to under treatment which may be a possible reason for resistance to drugs (Katzung 2011).

The result of this study is similar to the results obtained by other investigators in other countries particularly those from Africa on some poor quality drugs for malaria, the detection of substandard Artesunate tablets and a poorly formulated Amodiaquine tablets amongst the few sample brands studied highlights the need for increased drug surveillance and monitoring of the qualities of antimalarial medicines currently in use in order to prevent widespread treatment failure (Odunfa et al., 2009). Significant problems of substandard products exist within the drug distribution chains. Percentage failure of samples based on ingredient content cannot be ignored. In view of the potential danger that substandard antimalarials could already be posing in the fight against malaria, an intervention plan should be developed immediately. This could involve setting up quality surveillance systems within drug regulatory authorities in the region and supporting manufacturers to improve GMP compliance (Maponga and Ondari, 2003). Poor drug metabolism and drug – drug interactions have also been suggested in drug reactions (Ajuonuma et al. 2007) and Stevens Johnson's syndrome (Ajonuma and Chukwu 2000).

Interestingly, this study comes at a time when many are advocating the possibility of reintroducing Chloroquine phosphate in the treatment of non-falciparium malarial infection especially in SEA countries where other malaria parasites are the major causes of malaria and in consideration of other treatment uses of the Chloroquine phosphate as well.

In summary, Artemether Lumefantrine combination and Chloroquine phosphate tablets in this study showed good disintegration but had marginal and poor dissolution tests results respectively. The effects of these poor *in vitro* dissolution tests results on their *in vivo* metabolism and subsequent bioavailability, as well as their drug – drug interactions need to be thoroughly investigated to prevent the development of further drug resistance in these municipalities and possible life threatening drug reactions.

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The authors declare no conflict of interest.

Reference

Ajonuma LC, Chika LC. (2000) Outbreak of Stevens-Johnson syndrome among Filipino overseas contract workers using mebendazole for helminthiasis prophylaxis. Tropical Doctor 30(1):57

Ajuonuma, B.C., Ajuonuma, M.U, Uzo-Ngerem A., Ajuonuma, M.K. Ajuonuma F.O., Chukwu C.L., Ajonuma L.C., (2007) Sudden Enlargement of the Prostate in a Patient Taking Fansidar® for Malaria Drug Metabolism and Drug Interactions. 22, (4) 285–288.

Antimalarial medication, (2011). http://en.wikipedia.org/wiki/antimalarial_medication

British pharmacopoeia (2007). British Pharmacopoeia Commission, London, England, United Kingdom.

Caudron JM, Ford N, Henkens M, Mace´C, Kiddle-Monroe R, Pinel J. (2008). Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Tropical Medicine and International Health* 13 (8), 1062–1072.

Eduardo G, (2010), Malaria in the Philippines. *J. Philippines*, 10, 252

Geographical Distribution of malaria, Philippines (2010). http://www.dpd.cdc.gov/ dpdx/html/frames/m-r/malaria/body_Malaria_page2.htm

Antimalarial drug quality: methods to detect suspect drugs (2010) Harparkash Kaur , Michael D Green , Dana M Hostetler , Facundo M Fernández , Paul N Newton. *Therapy*, 7, 49-57.

Katzung B.G, Masters S.B, and Trevor A.J. (2009) *Basic and Clinical*
Pharmacology, (11th ed.). p905. Mac Graw Hill

Kaur K, Jain M, Reddy RP and Jain R (2010) Quinolines and structurally related heterocycles as antimalaraials. Eur. J. Med. Chem. 45; 3245 – 3264.

Lansang M. D. (1996). Epidemiological Aspect of Malaria in the Philippines.
Philippines journal Microbial Infec. Disease. 25 (2):s8.

Maponga C and Ondari C. (2003). The quality of antimalarials: A study in selected African countries. Geneva: World Health Organization, 2003. WHO/EDM/PAR/2003.4. http://apps.who.int/medicinedocs/pdf/s4901e/s4901e.pdf

Odunfa OO, Adegoke OA and Onaga IC, (2009). Pharmaceutical Equivalence of
Some Commercial Samples of Artesunate and Amodiaquine Tablets Sold in Southwestern Nigeria. Tropical Journal of Pharmaceutical Research, 8 (6): 491-499.

Roll Back Malaria, 2010. Roll Back Malaria Progress & Impact Series: *Saving Lives with Malaria Control: Counting Down to the Millennium Development Goals*.

United States Pharmacopoeia (USP) Rockville, MD: United States Pharmacopeia Convention; 2007

World Health Organization (1993). Counterfeit drugs. *Bull World Health Organ* 71, 464–466.

World Health Organization. (2011). Counterfeit and Substandard Drugs in
Myanmar and Viet Nam - Report of a Study Carried out in Cooperation with the Governments of Myanmar and Viet Nam – EDM Research Series N0. 029. (1999; 55 pages) http://apps.who.int/medicinedocs/en/d/Js2276e/6.2.html