STRENGTHENING OF NATIONAL CAPACITY IN IMPLEMENTATION OF ANTIMALARIAL DRUG QUALITY ASSURANCE IN THAILAND

Saowanit Vijaykadga[1], Sawat Cholpol[1], Saipin Sitthimongkol[1], Anusorn Pawaphutanan[1], Arunya Pinyoratanachot[1], Chaiporn Rojanawatsirivet[1], Rojana Kovithvattanapong[2] and Krongthong Thimasarn[3]

[1]Department of Disease Control, [2]Department of Medical Science, Ministry of Public Health, Thailand; [3]World Health Organization, South-East Asia Regional Office (SEARO), New Delhi, India

Abstract. Substandard and counterfeit pharmaceutical products, including antimalarial drugs, appear to be widespread internationally and affect both the developing and developed countries. The aim of the study was to investigate the quality of antimalarial drugs, *ie*, artesunate (ART), chloroquine (CHL), mefloquine (MEF), quinine (QUI), sulfadoxine/pyrimethamine (S/P) and tetracycline (TT) obtained from the government sector and private pharmacies in 4 Thai provinces: Mae Hong Son, Kanchanaburi, Ranong, and Chanthaburi. Three hundred sixty-nine samples of 6 antimalarial drugs from 27 government hospitals, 27 malaria clinics, and 53 drugstores, were collected. Drug quality was assessed by simple disintegration test and semi-quantitative thin-layer chromatography in each province; 10% passed, 100% failed and doubtful samples were sent to be verified by high performance liquid chromatography (HPLC) at the Thai National Drug Analysis Laboratory, (NL). Fifteen point four percent of ART, 11.1% of CHL and 29.4% of QUI were substandard. Based on the finding, drug regulatory authorities in the country took appropriate action against violators to ensure that antimalarial drugs consumed by malaria patients are of good quality.

INTRODUCTION

Malaria is a common problem on all international borders of the Greater Mekong Sub-region (GMS), where populations are highly mobile and have low socio-economic status. During the past decades, new strains of the particularly virulent form of *P. falciparum* have developed resistance to most antimalarial drugs available in this region. The problem is complicated by rapidly deteriorating drug resistance to *P. falciparum* parasites. Misuse of drugs and the use of substandard and counterfeit or fake medicines may have been contributing factors to drug resistance. Counterfeit/substandard drugs are one of the serious problems in the GMS and the issue has been documented (Newton *et al*, 2001, 2002; Passmore, 2001). There is also a need to improve the quality of antimalarial medicines manufactured in the region and to ensure that antimalarial drugs consumed by malaria patients are of good quality. Therefore, an effort was made to establish and strengthen the drug quality assurance system in this region. Thailand participated in this regional collaboration.

The objectives of this project were to strengthen national capacity in monitoring antimalarial drug quality as part of the antimalarial drug assurance (QA) system, and to investigate the quality of artesunate (ART), chloroquine (CHL), mefloquine (MEF), quinine (QUI), sulfadoxine/pyrimethamine (S/P), and tetracycline (TT).

Correspondence: S Vijaykadga, Bureau of Vector-Borne Disease, Department of Disease Control, Ministry of Public Health, 88/20 Tiwanond Road, Nonthaburi 11000, Thailand.
Tel: +66 (0) 2590-3126; Fax: +66 (0) 2591-8422
E-mail:saowanit@health.moph.go.th

MATERIALS AND METHODS

Drug sampling

The purpose of sampling in this project is to determine the incidence of good, as well as poor, quality antimalarial drugs in 4 sentinel sites by testing for appropriate labeling, the identity of the active pharmaceutical ingredients (API(s)), disintegration, and content of the API(s). The sampling team consisted of 1 technical officer from the Bureau of Vector-borne Diseases, 1 technical officer from the respective Regional Office of Disease Prevention and Control, 3 field malaria personnel (microscopist/house visitor) and 1 pharmacist from the Provincial Health Office. The team visited all registered private drugstores, groceries, government malaria clinics, and government hospitals. An amount of the available antimalarial drugs was purchased. The team carried out drug sampling three times a year in 4-month intervals (November 2003-October 2004) in Mae Hong Son (MHS), Kanchanaburi (KB), Ranong (RN, Thai-Myanmar border) and Chanthaburi (CHB, Thai-Cambodian border). The sampling team did not collect samples of drugs that did not contain the "identifiable" name of the drug product for its API(s).

Reference drugs

The active principles were obtained from SANAVITA Aktiengesellshaft & Co.D-59368 Werne Germany (artesunate 50 mg, chloroquine phosphate 250 mg, quinine sulfate 300 mg, sulfadoxine/pyrimethamine and tetracycline HCl 250 mg). The quality of the active principles of the reference tablets was controlled by thin-layer chromatography (TLC).

Drug analysis

The quality of the drug samples was evaluated in two steps. First, a screening test by GPHF-Minilab® (Jahnke, 2004) was carried out in each sentinel site. Second, dubious and failed samples were sent for verification at the Thai National Drug Analysis Lab (NL), Bureau of Drugs and Narcotics (BDN).

Visual examinations were undertaken for deficiencies of labeling, packaging and dosage forms, *eg*, missing or incorrect accompanying documents; packaging with incomplete, damaged, or missing labels, or labels with illegible print; broken container seals; defective dosage forms, such as cracked, broken, crushed, sticky, or non-uniform tablets.

The simple disintegration test is defined as the state in which no residue of the tablets or capsules, except fragments or undissolved coating, remain in the test solution. The method provides an estimated time (30 minutes) within which all uncoated tablets and capsules and all soluble, dispersible, effervescent, and film-coated tablets (*ie*, all quick-release formulations of a finished dosage form) should disintegrate in water at 37 $\pm$ 2 ˚C. If a drug product does not pass this test, there is a major defect in its quality because it will not dissolve, absorb and become bioavailable. The product can be rejected at this stage with no further investigation (Phanouvong *et al*, 2005).

Drug samples that passed the simple disintegration test were further analyzed by semi-quantitative thin-layer chromatography. The tablet form of ART, CHL, MEF, QUI, and S/P were ground to a fine power, and TT and the injection form of ART, QUI and CHL were diluted to concentrations of 5.0 mg/ml ART in methanol, 2.5 mg/ml CHL in water, 2.5 mg/ml MEF in methanol, 1.25 mg/ml QUI in methanol, 6.25 /0.3125 mg/ml S/P in methanol and 2.5 mg/ml TT in methanol, respectively. For each solution, 2 µl were spotted onto an aluminum chromatoplate coated with silica gel 60 F254 (stationary phase) (VWR International, Strasbourg, France) and perfectly sized (5x10 cm) to fit into the TLC chamber supplied. The mobile phase consisted of a mixture of ethylacetate/acetone/glacial acetic (v/v/v, 18:4:0.1) for ART, methanol/ethylacetate/20% NH_4OH solution (v/v/v, 40:10:10) for CHL, ethylacetate/methanol/ammonia solution (v/v/v, 16:4:3) for MEF, methanol/20% NH_4OH solution (v/v, 40:1) for QUI, methanol/ethylacetate (v/v, 1:3) for S/P, and methanol/acetone/aqueous edetate/Mg^{2+}solution (v/v/v,10:5:5) for TT. The spots corresponding to each sample were revealed by exposing dry TLC plate to 5% methanolic sulfuric acid solution (19 ml of methanol with 1 ml of 96% sulfuric acid in the Petri dish), hot plate for ART and TT, and ultraviolet light (254 nm and/or 365 nm) for CHL, QUI, and S/P. The travel distances of the spots were expressed as the relative retention factor (R_f value), defined as the distance covered by the mobile phase. Each test was run against the reference tablets diluted to the standard working solution, defined as the upper limit set at 100% (4.0 mg/ml for ART, 2.0 mg/ml for CHL, 2.0 mg/ml for MEF, 1.0 mg/ml for QUI, 5.0/0.25 mg/ml for S/P, and 2.0 mg/ml for TT), and the lower limit set at 80% (5.0 mg/ml for ART, 2.5 mg/ml for CHL, 2.5 mg/ml for MEF, 1.25 mg/ml for QUI, 6.25 /0.3125 mg/ml for S/P, and 2.5 mg/ml for TT). The range of 80-100% ($\pm$ 10% possible error due to visual inspection) is considered accurate enough to determine drug quality by thin-layer chromatography (TLC) (Basco *et al*, 2004; Phanouvong *et al*, 2005). The 100% doubtful, 10% of failed samples passed by GPHF-Minilab® test were sent to the NL for verification using disintegration test and high-performance liquid chromatography (HPLC).

Data interpretation

A counterfeit medicine, as defined by the WHO, is a drug that is deliberately and fraudulently mislabeled with respect to identity and/or source (WHO, 1999). A counterfeit drug can apply to both branded and generic products, including products with the correct or wrong ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging. A substandard product is a legal branded or generic product that does not meet international standards for quality, purity, strength, or packaging.

RESULTS

A total of 369 test samples consisted of 53 samples of ART tablets and 36 samples of MEF tablets (12 lots in 2 brands) that had been collected from government hospitals and malaria clinics, 86 samples of CHL tablets, 88 samples of QUI tablets, 13 samples of S/P tablets and 93 samples of TT capsules collected from hospitals, malaria clinics, and drugstores. There were 11 samples of ART injections, 5 samples of CHL injections and 2 syrups, and 32 samples of QUI injections. The distribution of drug samples broken down by lot and brand are shown in Table 1.

The results of quick analysis at the sentinel sites showed that 15 samples failed in the disintegration test and 100% passed for TLC. The 79 samples of the passed drug samples and doubtful samples after the quick analysis were sent to the NL for verification; the results are shown in Table 2.

Artesunate

The 53 ART samples were collected, all of them passed visual/physical examination and TLC test but 2 of 13 (15.4%) samples were substandard with HPLC, containing 89.8% and 88% ART (specification 99.0-110.0% la.). These failed samples had been collected from Chanthaburi and Ranong provinces, and had 1 and 2 months remaining, respectively before the expiry date.

Chloroquine

Eighty-six CHL phosphate samples (both tablets and parenteral preparations) were collected from hospitals, malaria clinics, and drugstores. Nine samples (10.5%) failed the disintegration test in the GPHF-Minilab®. The 18 samples were sent to be verified; 2 (11.1%) of these samples were substandard, with disintegration in > 30 minutes.

Mefloquine

Thirty-six MEF samples were collected. There were neither substandard nor fake/counterfeit drugs. Nine samples were randomly sampled for verification at the NL; all (100%) showed concordance between GPHF-Minilab® (TLC) and HPLC results.

Quinine

Eighty-eight quinine sulfate and quinine dihydrochloride samples were collected; 4 (4.5%) failed the disintegration test with GPHF-Minilab®; 17 were randomly selected and sent to be verified, whereas 5 (29.4%) were substandard, with disintegration time > 30 minutes.

Sulfadoxine/pyrimethamine

Thirteen S/P samples were collected, and none was substandard or fake/counterfeit; 3 samples were selected to be verified at the NL. The results of GPHF-Minilab® (TLC) and HPLC agreed.

Table 1
Summary of drug samples by lot and brand.

Name	No. of samples	No. of lot	No. of brand
Artesunate, 50 mg	42	8	2
Artesunate injection	11	5	1
Chloroquine phosphate, 250 mg	81	59	9
Chloroquine injection	5	5	2
Mefloquine hydrochloride, 250 mg	36	12	2
Quinine sulfate, 300 mg	56	41	13
Quinine dihydrochloride injection	32	21	4
Sulfadoxine/pyrimethamine	13	5	1
Tetracycline (capsule)	93	77	21

Table 2
Summary of samples tested at sentinel site and national laboratory.

Location/drug	No. of samples tested/failed using basic tests at sentinel site (failed samples in percent)	No. of samples tested/ failed at NL (failed samples in percent)
Artesunate	53/1 (1.9)	13/2 (15.4)
Chloroquine	86/9 (10.5)	18/2 (11.1)
Mefloquine	36/0	9/0
Quinine	88/4 (4.5)	17/5 (29.4)
Sulfadoxine/pyrimethamine	13/0	3/0
Tetracycline	93/1 (1.1)	19/0

Tetracycline

Ninety-three TT samples were collected. One sample (1.1%) failed the disintegration test with GPHF-Minilab®. Nineteen samples were verified at the NL, where the screening test results were confirmed by HPLC. None of the samples tested was substandard.

DISCUSSION

The primary purpose of this project was to strengthen the capacity of the country's field-level malaria officers in examining the quality of available antimalarial medicines, rather than searching for counterfeit drugs. However, the study sites were selected based upon malaria endemicity, high consumption of antimalarial drugs, and utilization of artemisinin-based combination therapy (ACT), which is presumably a target for counterfeiting. The four study sites: MHS, KB, RN and CHB provinces are sentinel sites for drug-resistance monitoring, which has been carried out for several years. The first 3 sentinel sites lie along the Thai-Myanmar border, while the 4th lies along the Thai-Cambodian border. It was assumed that the quality of drugs at the periphery and each remote border area would not be as good as in urban areas, where Thailand's Food and Drug Administration (FDA) inspections can be performed more regularly.

The survey teams consisted of pharmacists from Provincial Health offices, malaria technical officers from the Bureau of Vector-borne Diseases and technical officers from the Regional Offices of Disease Prevention and Control who were trained to operate the GPHF-Minilab® test kits. This is the first time in the history of the Thai Malaria Control Program and FDA that malaria officers not involved in drug analysis of any kind can be trained to perform drug screening tests. It is well known that malaria in this country is not only a forest-related disease but also a border disease where ethnic minority groups or illegal migrant laborers are the major population at risk. The nature of the disease has made the population at risk vulnerable to the disease and at the same time potential victims of substandard and counterfeit drugs. This study proved that drug sampling and screening tests could be performed effectively by malaria officers with minimal training.

Antimalarial drugs were collected officially from the private and government sectors by the survey teams. All drug sources were informed about the project prior to drug collection; therefore, counterfeit drugs known by drug suppliers were expected to be excluded from the project. Theoretically, ART and MEF can be collected only from government healthcare centers, such as malaria clinics and government hospitals, because of their controlled distribution. Neither drug should be made available over the counter in any drugstore, drug vendor, private clinic or even private hospital, without special authorization from the Department of Disease Control. This strict control of antimalarial drug distribution is part of national drug policy, to prevent the misuse of antimalarials. The survey teams searched for these two drugs, to check indirectly whether their distribution was actually controlled in practice. The results showed that neither drug was available in any drug outlet or study site.

Quality analysis of all ART and MEF samples showed the quality met the standards. No counterfeit drugs were found. This may be because these two drugs were only found in the public sector, hospitals and malaria clinics. The team found some doubtful unlabeled samples that might be ART; however, they were excluded from the study because of the project methodology. This is why this study could not detect counterfeit samples compared with other studies (Newton *et al*, 2001; Dondorp et al, 2004).

The TLC method was less sensitive and less specific than HPLC analysis, so the result may underestimate the problem of substandard drugs (Basco, 2004). Chemical analysis of ART samples revealed that two samples collected from malaria clinics in CHB and RN provinces were classified as "substandard" when analyzed with HPLC at NL [API(s) 89.9 and 88%, respectively]. Both failed samples might have been partially degraded because of their expiry within 1-2 months. ART has a relatively short shelf-life and easily degrades at normal room temperature (>35 °C) at malaria clinics, compared with air-conditioned storage rooms in hospitals, where they are maintained by qualified pharmacists. According to the present study, ART would degrade more easily in normal room conditions than when kept in a hospital. Therefore, its shelf life in normal room conditions would be shortened to 2.5 years. This issue needs further study. It is strongly suggested that efforts be made to improve storage conditions for this drug in peripheral facilities.

In 2004, the FDA reported that the physical inspection and TLC test (GPHF-Minilab®) analysis of 6 ART and 1 MEF samples collected from the black market along the Thai-Myanmar and Thai-Cambodian borders were "genuine" drugs (Thitikornkowit D, personal communication). In contrast, Newton *et al* (2001) and Dondorp *et al* (2004) reported that 11 and 27%, respectively, of ART samples from the black market in Tak Province were counterfeit.

The other drugs--QUI, CHL, S/P and TT...which are permitted to be sold in grade-one drugstores

(operated with pharmacists on duty) were still sold in second-grade drugstores (without pharmacists on duty), and groceries. They were bought occasionally from both types of drugstores, 100 to 200 tablets at a time and mixed up in one bottle without labeling of the scientific drug name, manufacturer, manufacture date, or expiry date. Drugs bought from groceries were classified as unidentifiable, but not included in this study. The GPHF-Minilab® results showed that 9 samples of CHL and 4 samples of QUI failed the simple disintegration test. By comparison, the Department of Medical Science revealed that 2 samples of CHL and 5 samples of QUI failed the same test. Most of these drugs were in a coated tablet form. The failed CHL samples were manufactured by two different manufacturers, while the failed QUI samples were produced by 4 different manufacturers. These findings were similar to those of Thailand's FDA (Thitikornkowit D, personal communication). Recently, in May 2005, the FDA ordered two manufacturers to withdraw their products from the market due to their being substandard. The finding from the present study confirmed that the substandard drugs (QUI and CHL) were manufactured by these 2 manufacturers. Hence, drug regulatory action has not been taken. This finding prompts action by the FDA.

In addition, the S/P and TT samples met standard levels. On the contrary, Thailand's FDA reported that 6.8% (7/103) of TT sold in drugstores or groceries were substandard (Thitikornkowit D, personal communication). In general, TT is a broad-spectrum antibiotic sold in all types of drugstores and groceries where the patient can easily purchase them for non-malaria treatments. Especially in grade-one drugstores, the staff suggest that customers use QUI with TT to treat malaria. Since most Thai people are likely to self-treat, small amounts of QUI, S/P and TT are bought mainly for treatment of fever or for prophylaxis purposes (Sringernyuang, 1995).

Surprisingly, S/P tablet and CHL injection form, which are no longer used in the government sector because of their inefficacy, were still sold in all 4 studied areas. Neither is effective against falciparum malaria and patients who are infected with vivax malaria can be treated with the oral form. Therefore, the availability of these two products in the market should be brought to the attention of the FDA, for consideration as to whether these drugs should be made available in the market or their registration should be cancelled.

Many drugstores have been established in the border districts of the 4 study areas, of which only a small fraction has been registered as under the control of qualified pharmacists (grade one). Registered drugstores without pharmacist (grade two) in many provinces of Thailand are still selling "Ya chud", a set combination of pills in plastic bags that may or may not contain antimalarial drugs for treating malaria. On the other hand, pharmacists in registered grade-one drugstores refuse to sell "Ya chud" and give appropriate advice to clients who ask for it. The type-two and unregistered drugstores in border districts may also be main sources of counterfeit drugs, which are smuggled to Thailand's neighbors. Moreover, there is strong evidence from several studies that type-two drugstores and unregistered drugstores fail to provide appropriate advice to clients, leading to the misuse of drugs, which does not normally happen with registered drugstores.

The current project has gathered basic information and problems related to antimalarial drugs, *eg* counterfeit drugs, quality, shelf life, drugstores, and pharmacists, which have a direct impact on improving antimalarial drug control and drug use. During project implementation, malaria-clinic and provincial-level staff were trained with general knowledge about antimalarial drugs, drug analysis, and sensible drug practices. These trained personnel should add value to the Malaria Control Program and the activities of Thailand's Food and Drug Administration.

Conclusion and recommendation

Although counterfeit antimalarial pharmaceutical products were not detected during the one-year monitoring period, other problems were found. A number of antimalarial drugs were of substandard quality, while certain drugs that are no longer recommended for malaria treatment are still available in the market. However, this project has greatly increased awareness regarding the quality issue among concerned officers.

Therefore, further suggested activities are as follows: 1. conduct continuous training programs for officers on efficient and effective drug procurement and management; 2. expand drug quality assurance monitoring in wider geographical areas; 3. build collaboration among malaria units, drug-analysis laboratory units and drug regulatory agencies at all levels for joint drug-quality monitoring programs. Both secret sampling and open sampling procedures should be employed; 4. promote public understanding of the danger of self-medication for malaria infections.

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