CHLOROQUINE CONTENT IN TABLETS, SYRUPS AND INJECTIONS OF SOME COMMON BRANDS IN NIGERIA

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ABSTRACT

Counterfeit and poor quality antimalarial drugs pose a serious threat towards the eradication of malaria, the greatest public health problem in subsaharan Africa. The high cost of Artemisinin Combination Therapy (ACT) is creating a huge market for counterfeit antimalarials which has lead to a dramatic rise in poor quality and counterfeit chloroquine dosage forms in subsaharan Africa. The aim of the present study was to evaluate the percentage drug content in three dosage forms of chloroquine, viz: tablets, syrups and injections of some common brands in Nigeria. The organoleptic properties, identity of the drugs, weight uniformity, friability, dissolution and disintegration of the drug samples were also evaluated using official methods. Results obtained revealed that all the drug samples qualitatively contained the active ingredient. Also, all the tablet samples passed the uniformity of weight, dissolution and disintegration tests; and had uniform organoleptic properties. However all the injection samples did not contain the active ingredient in the required amount as stated in official compendia. The result of this study has shown that despite the efforts of the National Agency for Food, Drug Administration and Control (NAFDAC), fake and substandard anti malarials are still in circulation in Nigeria.

KEYWORDS: Chloroquine, content, tablets, syrups, injections, Nigeria.

INTRODUCTION

The proliferation of counterfeit and substandard pharmaceutical drugs is a global phenomenon although it is largely acknowledged as a problem of the developing world
(Clarke, 2002). About 15% of all drugs in circulation worldwide are believed to be fake, with the figure rising to 50% in sub-Saharan Africa and some parts of Asia (Hall, 2005). Pharmaceutical drugs are attractive candidates for producers involved in this illegal trade mainly because the benefits are immense and the risks very limited. Fake drugs are easily transportable, have high value per unit and above all, their quality cannot be scientifically or legally assessed without a quality control testing laboratory (Ambroise – Thomas, 2012).

Since 2001, the National Agency for Food, Drug Administration and Control (NAFDAC) the Nigerian equivalent of the Food and Drug Administration in USA has been detecting with increasing frequency counterfeit drugs used for the treatment of potentially fatal tropical diseases such as malaria. Despite efforts by the World Health Organization (WHO) and individual governments malaria continues to be a major public health problem with 300 – 500 million clinical cases annually out of which more than 1 million people die of the disease mostly children below five and pregnant women (Okenu, 1999). The control of malaria still depends on the use of effective antimalarial drugs and bednets. However during the past three decades malaria control has been hampered by an increase in the prevalence of drug resistant malarial parasites. In 1999 the World Health Organization (WHO) recommended artemisinin based combination therapy (ACTs) in the management of acute uncomplicated malaria. Most African governments south of the Sahara have adopted this policy. Despite this, most people still depend on chloroquine for the treatment of malaria because it is cheap, readily available and they are familiar with the drug.

The use of counterfeit antimalarial drugs has led to mass deaths in Nigeria and elsewhere. In 1947, 14 children died after being administered fake chloroquine phosphate injections while 109 children lost their lives after being administered fake paracetamol syrup in 1990 (Aluko, 1994). Since counterfeit antimalarials most often contain non or suboptimal amounts of the active ingredients, quantification of chloroquine in tablet, syrup and injection is necessary.

MATERIALS AND METHODS

Chemicals

All the chemicals used in this study were of analytical grade. They were as follows: Potassium hydroxide, nitric acid, silver nitrate, trinitrophenol, sulphuric acid, chloroform, hydrochloric acid, potassium – mercuric iodide solution, ammonium molybdate, sodium hydroxide, acetic acid (glacial), dioxane, perchloric acid. Water used was distilled.
Table 1. Label information on chloroquine tablets, syrups and injections.

<table>
<thead>
<tr>
<th>S/n</th>
<th>Brand code</th>
<th>Dosage form</th>
<th>Labeled dose</th>
<th>Manuf. date</th>
<th>Exp. date</th>
<th>NAFDAC No.</th>
<th>Batch No.</th>
<th>Country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CQT1</td>
<td>Tablet</td>
<td>250 mg</td>
<td>08 200</td>
<td>07 201</td>
<td>04 - 0284</td>
<td>IZ 972</td>
<td>Nigeria.</td>
</tr>
<tr>
<td>2</td>
<td>CQT2</td>
<td>Tablet</td>
<td>250 mg</td>
<td>06 2012</td>
<td>05 - 2016</td>
<td>04 - 8186</td>
<td>I2066</td>
<td>Nigeria.</td>
</tr>
<tr>
<td>3</td>
<td>CQT3</td>
<td>Tablet</td>
<td>250 mg</td>
<td>04 - 2012</td>
<td>03 - 2015</td>
<td>04 - 2102</td>
<td>2D851030</td>
<td>Nigeria.</td>
</tr>
<tr>
<td>5</td>
<td>CQT5</td>
<td>Tablet</td>
<td>250 mg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>CQS1</td>
<td>Syrup</td>
<td>50 mg</td>
<td>10 12</td>
<td>10 15</td>
<td>04 - 3753</td>
<td>L963R</td>
<td>Nigeria.</td>
</tr>
<tr>
<td>7</td>
<td>CQS2</td>
<td>Syrup</td>
<td>50 mg</td>
<td>4 - 2011</td>
<td>5 - 2014</td>
<td>04 - 3597</td>
<td>2110111</td>
<td>Nigeria.</td>
</tr>
<tr>
<td>8</td>
<td>CQS3</td>
<td>syrup</td>
<td>50mg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>CQS4</td>
<td>syrup</td>
<td>50mg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>CQS5</td>
<td>syrup</td>
<td>50mg</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>CQL1</td>
<td>Injection</td>
<td>40 mg/5 ml</td>
<td>06 / 2011</td>
<td>05/2014</td>
<td>04 - 3805</td>
<td>NA</td>
<td>India.</td>
</tr>
<tr>
<td>12</td>
<td>CQL2</td>
<td>Injection</td>
<td>322 mg/5 ml</td>
<td>08 2011</td>
<td>07 2014</td>
<td>047397</td>
<td>110801</td>
<td>China.</td>
</tr>
<tr>
<td>13</td>
<td>CQL3</td>
<td>Injection</td>
<td>322 mg/5 ml</td>
<td>06 2011</td>
<td>05 2014</td>
<td>04 3339</td>
<td>1106C8</td>
<td>China.</td>
</tr>
<tr>
<td>15</td>
<td>CQL5</td>
<td>injection</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>China.</td>
</tr>
</tbody>
</table>

Instruments

Analytical balance, Monsanto hardness tester, B and T friability tester, Avis single unit disintegration test apparatus, Avis single unit dissolution test apparatus, UV/Vis spectrophotometer, water bath, separating funnel, burettes, conical flasks, beakers.

Pharmaceutical drugs

Three dosage forms: tablets, syrup and injections of chloroquine were bought without prescription from different pharmacy shops and patent medicine retail out fits in Owerri and Elele. The drugs were coded and examined for batch numbers, NAFDAC registration status, manufacturer’s names, addresses and shelf life (Table 1).

Organoleptic properties

The following organoleptic properties were assessed by 3 independent persons: shape, colour, taste and smell. A majority decision was taken as positive.

Identification tests

The method used for the identification of chloroquine was as outlined in the basic tests for pharmaceutical dosage forms (WHO, 1991).
Weight variation
20 tablets of each brand were weighed individually with an electronic balance (Brand of electronic balance) and the mean and standard deviation calculated. The percentage deviation was also determined.

Hardness/Crushing Strength Test
The Monsanto hardness tester was used and the result expressed in KGF (Monsanto). For each sample, ten tablets were used. Each of the tablets is placed in the lower plunger and adjusted to hold the tablets between the lower and upper plunger. The leader was adjusted to zero, the bolt was tamed until the tablets broke and the readings obtained from the reader. The mean hardness was determined in each case.

Friability Test
The Erweka friabilator was used. The hollow chamber was opened and cleaned. Ten tablets from each sample were chosen at random and the weight determined using weighing balance. The tablets were placed in the chamber, closed and tightened properly. The instrument was switched on and allowed to rotate for 4 minutes at 25 rpm. The tablets were removed, redusted and reweighed. The difference in weight was determined and expressed as percentage which represents the friability. The same procedure was repeated for ten tablets for each of the sample.

Disintegration Time Test
The Erweka disintegration unit was used to determined disintegration time. A 0.1M hydrochloric acid maintained at 3±1°C was used as a disintegration fluid. One tablet was placed into each of the six baskets. The motor was switched on and the disintegration time determined. The same was repeated with six other tablets from each sample. The disintegration time was the time no residue of the tablet remained on the mesh basket, expect fragments of undissolved coating remains. The mean disintegration time for each of the sample was determined.

Dissolution Rate Test
The dissolution unit used was a beaker containing 900ml of 0.1N HCl which is the dissolution medium and maintained at a temperature of approximately 37°C. A magnetic stirrer was dropped into the medium and the tablet to be assayed was put into a 20 mesh basket immersed in the beaker. At every 5 minutes interval, 5ml aliquot was withdrawn from
the beaker and immediately replaced with 5ml of 0.1N HCl after 1 hour. The absorbance of each of the aliquot withdrawn was measured. The same procedure was carried out on other brands (BP, 2005).

**Assay of chloroquine tablets**
20 tablets of chloroquine phosphate were weighed and powdered and an amount equivalent to 0.23 g was accurately weighed and dissolved in 20 ml of glacial acetic acid with the aid of heat. It was cooled and 20 ml of dioxane added. It was titrated with 0.1 M perchloric acid. Each ml of 0.1 M perchloric acid is equivalent to 25.79 mg of \( C_{18}H_{26}ClN_3\cdot2H_3PO_4 \).

**Assay of chloroquine syrup and chloroquine injection**
An amount each of chloroquine syrup and chloroquine injection equivalent to 0.3 g of chloroquine were placed in two separate 250 ml separating funnels containing 15 ml of water and 3 ml 2M NaOH added to make the solution alkaline. The content of each separating funnel was extracted three times with 15 ml portions of chloroform (Ofokansi et al., 2009). The pooled chloroform extracts were titrated with 0.1 M perchloric acid using crystal violet as indicator.

**RESULTS AND DISCUSSION**
The illegal production, sale and distribution of fake pharmaceutical drugs is a booming trade representing more than 50% of the pharmaceutical market in Africa and evaluated to worth several billion dollars (Ambroise – Thomas, 2012). Fake anti malarial drugs have led to many deaths resulting from treatment failure and drug resistance. The tragedy of fake drugs is a global problem but is rife in the developing world where drug distribution is chaotic.

A total of 15 samples of chloroquine phosphate products were analysed in this study. All the samples were within their shelf life at the time of the study. The tablets and syrups were manufactured in Nigeria while the injections originated from India and China. One tablet, three syrup and one injection samples of chloroquine lacked manufacturing and expiry dates, NAFDAC and batch numbers. Samples CQL4 and CQL5 of chloroquine injections lacked the lable dose. Most of the inscriptions on the injections were in Chinese. The organoleptic properties of chloroquine tablets showed they all complied with the British Pharmacopoeia (BP, 1993) standards. The tablets were cream or white in colour, round and intensely bitter (Table 2).
Table 2. Organoleptic properties of chloroquine tablets.

<table>
<thead>
<tr>
<th>Brand Code</th>
<th>Colour</th>
<th>Shape</th>
<th>Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ1</td>
<td>Cream</td>
<td>Round</td>
<td>Intensely bitter</td>
</tr>
<tr>
<td>CQ2</td>
<td>White</td>
<td>Round</td>
<td>Intensely bitter</td>
</tr>
<tr>
<td>CQ3</td>
<td>White</td>
<td>Round</td>
<td>Intensely bitter</td>
</tr>
<tr>
<td>CQ4</td>
<td>White</td>
<td>Round</td>
<td>Intensely bitter</td>
</tr>
<tr>
<td>CQ5</td>
<td>White</td>
<td>Round</td>
<td>Intensely bitter</td>
</tr>
</tbody>
</table>

Table 3. Physicochemical properties of chloroquine tablets.

<table>
<thead>
<tr>
<th>Brand Code</th>
<th>W (mg)</th>
<th>$D_T$(Mins)</th>
<th>$D_{45}$(Mins)</th>
<th>% DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQT1</td>
<td>315 ± 3.1</td>
<td>2.50</td>
<td>90.5</td>
<td>97.8</td>
</tr>
<tr>
<td>CQT2</td>
<td>310 ± 6.5</td>
<td>4.0</td>
<td>101.2</td>
<td>102.1</td>
</tr>
<tr>
<td>CQT3</td>
<td>322 ± 7.1</td>
<td>3.5</td>
<td>98.4</td>
<td>95.5</td>
</tr>
<tr>
<td>CQT4</td>
<td>402 ± 5.1</td>
<td>2.7</td>
<td>101.1</td>
<td>105.2</td>
</tr>
<tr>
<td>CQT5</td>
<td>399 ± 5.5</td>
<td>3.4</td>
<td>99.5</td>
<td>101.5</td>
</tr>
</tbody>
</table>

$W$ = average weight of tablet $D_T$ = Disintegration time $D_{45}$ = % dissolution in 45 mins

DC = % Drug content.

Table 4. Percentage drug content in chloroquine tablets, syrups and injections.

<table>
<thead>
<tr>
<th>Brand Code</th>
<th>Labeled Strength (mg)</th>
<th>Actual Strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQT1</td>
<td>250</td>
<td>97.8</td>
</tr>
<tr>
<td>CQT2</td>
<td>250</td>
<td>102.1</td>
</tr>
<tr>
<td>CQT3</td>
<td>250</td>
<td>95.5</td>
</tr>
<tr>
<td>CQT4</td>
<td>250</td>
<td>105.2</td>
</tr>
<tr>
<td>CQT5</td>
<td>250</td>
<td>101.5</td>
</tr>
<tr>
<td>CQS1</td>
<td>50</td>
<td>99.5</td>
</tr>
<tr>
<td>CQS2</td>
<td>50</td>
<td>100.9</td>
</tr>
<tr>
<td>CQS3</td>
<td>50</td>
<td>102.7</td>
</tr>
<tr>
<td>CQS4</td>
<td>50</td>
<td>103.1</td>
</tr>
<tr>
<td>CQS5</td>
<td>50</td>
<td>101.5</td>
</tr>
<tr>
<td>CQL1</td>
<td>40</td>
<td>59.7</td>
</tr>
<tr>
<td>CQL2</td>
<td>322</td>
<td>66.1</td>
</tr>
<tr>
<td>CQL3</td>
<td>322</td>
<td>89.5</td>
</tr>
<tr>
<td>CQL4</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>CQL5</td>
<td>NA</td>
<td>-</td>
</tr>
</tbody>
</table>

CQT = Chloroquine tablet CQS = Chloroquine syrup CQL = Chloroquine injection.

All the drug samples irrespective of the dosage form contained the active ingredient as revealed by the colour tests. The World Health Organization’s Basic Tests for pharmaceutical drugs (WHO, 1991) was adopted for the identity tests of chloroquine. The procedures listed are particularly useful in the third world where sophisticated laboratory facilities for drug
testing are difficult to come by. Results of the physicochemical properties of the drugs are summarized in table 3.

All the 5 samples of chloroquine tablets and syrups were locally manufactured. The weight uniformity, disintegration time, dissolution rate and percentage content of active ingredient were all within the pharmacopoeial range. All the 5 samples of chloroquine injection failed the percentage content requirement as stipulated by the British Pharmacopoeia (Table 4). The titrimetric method of assay was employed to determine the percentage drug content because of its precision and accuracy (Watson, 2000). A major problem with the treatment of malaria is the high level of treatment failures resulting from the high prevalence of counterfeit drugs (Hall et. al., 2006; Newton et. al., 2006; and Bate et. al., 2008).

In conclusion, despite the efforts of NAFDAC to rid the country of substandard and fake pharmaceutical drugs, fake anti malarial drugs which are imported are still in circulation.

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