ISSN 2349-7203

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

HUMAN

Human Journals
Research Article
June 2016 Vol.:6, Issue:3

Quality Assurance Testing of Chloroquine Tablets in Northern Nigeria

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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Submission: 5 June 2016
Accepted: 10 June 2016
Published: 25 June 2016

Keywords: Chloroquine tablet, Quantitative Assay, Nigeria

ABSTRACT

Quantitative drug assays measure the actual amounts of active ingredients in a tablet sample. It is the most important assessment tool in tablet technology that determines the percentage of substandard, fake and adulterated drugs. This study is aimed at assessing the quality of chloroquine tablets in Northern Nigeria by determining their active chloroquine content quantitatively. Twenty tablets from each coded samples were weighed and homogenized into fine powder at which 0.5g of CQ phosphate (or sulphate) was treated with 20 ml of 1M sodium hydroxide and thereafter extracted with chloroform. About 40 ml of anhydrous glacial acetic acid were added to the concentrated chloroform extract and titrated with 0.1M Perchloric acid. The amounts of chloroquine phosphate or sulphate as contained in 0.5g of their respective powders were calculated by multiplying these factors with the respective volumes of Perchloric acid utilized during the titrations. In this study, only 56.77% of the 146 samples contained standard CQ amounts of 92.5% - 107.5%, the remaining 43.23% had values outside this range and their mean value was 70.61±10.02% (176.53±25.05mg). State A had the highest failure rate with 65.71% followed by states B and C with 48.65% and 40.38% respectively. Tablet samples, the origin of which was traced to South-Eastern Nigeria or abroad had poor quality as against those manufactured in the North-Western and South- western regions of Nigeria. The actual chloroquine content in a tablet was evaluated across the study states and significant number of the study sample did not comply with the set standard, leading to drug pressure and subsequent resistance among malaria parasites in northern Nigeria.

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INTRODUCTION

In formulation of tablets, other substances generally referred to as excipients are often incorporated to aid the processing of tablets such as flowability, compressibility, elegancy, delivery or release of its active component so as to make it bioavailable.[1-4] Countries have individual national legal requirements, which must be met by each manufacturer, with the view of obtaining the desired qualities of pharmaceutical products that is being presented to users.[4] These legal requirements are backed up by pharmacopoeias, which provide chronological procedures for the manufacturing of specific quality products.[5] States should strictly adhere to this resolution and all the procedures thereof are adopted and applied by the manufacturers of number states. In addition to these pharmacopoeias, statutory bodies and professionals are charged with specific responsibilities for effecting compliance by the manufacturer.[3, 5] These statutory bodies, through the use of trained personnel, ascertain the qualities of pharmaceutical products by inspection, sampling to analyze the active ingredients and excipients, supervision of distribution, withdrawal of expired or contaminated products, ensuring of good storage facilities both at the warehouse of the manufacturer and medical or drug stores at tertiary/secondary and primary levels of the health care system.[3, 5] Therefore, quality assessment is necessary to ensure that the product being taken by a patient contains the required amounts of active ingredients and to ensure their bioavailability.

MATERIALS AND METHODS

Quantitative analysis for chloroquine content

Twenty (20) tablets from each coded samples were weighed and homogenized into fine powder. Of the powder, a quantity containing 0.5g of CQ phosphate (or sulphate) was treated with 20 ml of 1M sodium hydroxide and thereafter extracted with 4 x 25 ml of chloroform. The 4 chloroform extracts were pooled and evaporated to a volume of about 10 ml. About 40 ml of anhydrous glacial acetic acid were added to the concentrated chloroform extract and titrated with 0.1M Perchloric acid as described for non-aqueous potentiometric titrations. The temperature of the titrant at the time of standardization was measured. Any change in the two temperatures meant a change in volume which was corrected by Vc = Vd [1 + 0.0011 (tl-t2)], where Vc = corrected volume and Vd = determined volume. As stated in official monographs, each 1 ml of

0.1M Perchloric acid is equivalent to 0.02579g of CQ phosphate or 0.2090g of CQ sulphate. The amounts of chloroquine phosphate or sulphate as contained in 0.5g of their respective powders were calculated by multiplying these factors with the respective volumes of Perchloric acid utilized during the titrations.

Standardization of Perchloric acid

The quantitative assay of chloroquine requires the use of standardized Perchloric acid for titration. About 0.5g of potassium hydrogen phthalate R, previously dried at l20°C for 2 hours, was accurately weighed and dissolved in 50 ml glacial acetic acid (GAA) under mild heating conditions. The obtained solution was allowed to attain room temperature. About two drops of crystal violet / acetic acid indicator were added and then titrated with 0.1M Perchloric acid. Changes in pH were noted. The volume of Perchloric acid that brought about a change in colour from violet (basic) to bluish-green (neutral) was recorded. The experiment was repeated and the average volume of 0.1M Perchloric acid required to neutralize the potassium hydro phthalate was determined. The normality of the Perchloric acid was calculated from the relationship, $N_1V_1 = N_2V_2$: This standardized 0.1M Perchloric acid was used for non-aqueous potentiometric titration.[6, 7]

RESULTS

Quantitative CQ assay is presented in Table 1, Figures 1 and 2. Figure 1 shows that in states A, B, C and D, 12(34.3%), 19(51.4%), 31(59.6%) and 18(81.8%) of the samples, respectively passed the assay tests. Thus their assay values ranged between lower and upper limits of 92.5 - 107.5%. The remaining samples from the states in the same order failed the tests. On the other hand, 2(5.7%), 2(5.4%), 6(11.54%) and 2(9.1%) of the samples marginally failed the assay tests by lying 1-2% below the lower limit. Of all the states, only state A significantly failed the assay tests with 3 samples lying above the upper limits. On the whole, state A had the highest failure rate of 65.71%, followed by states B, C and D with 48.65%, 40.38% and 18.18% respectively. State D performed most creditably with a passing rate of 81.82% of the samples. Figure 2 shows that the mean CQ content per average tablet in states A, B, C and D, were found to be 188.36±68.69 mg, 208.67±52.89 mg, 211.48±53.17 mg and 233.75±13.65 mg respectively, corresponding to 75.34±27.48%, 83.47±21.16%, 84.59±21.27% and 93.5±5.46% of expected CQ

content respectively. From these mean values, it can be seen that only state D complied with the minimum requirements as stated in the standard literature (BP, 1988).[7] The result of this study also revealed that there was no statistical significant difference in the content of active chloroquine in tablets sampled from pharmaceutical chemist and those sampled from patent medicine stores ($p>0.05$) (Table 1).

DISCUSSION

Quantitative drug assays employed to measure the actual amounts of active CQ in a tablet sample in this study is often regarded as the most important quality assessment in tablet technology because tablets may be 100% bioavailable but the amount of active ingredient may be insufficient.[3] This finding is in agreement with several literature reports in which similar observations were made.[1-3] About 43.23% of all samples did not contain the expected quantity of 92.5% - 107.5% active CQ.[7] Thus in the study area as a whole, only 56.77% of the samples passed the assay tests. This means such substandard products could not release therapeutic amounts of CQ moieties and therefore only sub-therapeutic amounts will be available in the blood. This situation is disturbing because such products will not be effective. Instead, they only select resistant strains from a population that is otherwise sensitive.[2, 8] State A registered the highest failure rates of samples. This state is therefore likely to experience drug resistance as opposed to state D which had the least failure rate of 18.18%.[8] State D performed very well and the average tablet contained 233.75 mg CQ salts. In contrast, only 188.36 mg were found in the average tablet from state A. On comparison of the two states, state A was found to be significantly different from state D ($p<0.01$). In contrast, the values for state pairs A & B, B & C, A & C and C & D were not significantly different from each other ($p>0.05$ for all the pairs), while values for states B & D were significantly different ($p<0.05$). There was no statistical significant difference in the actual content of active chloroquine in tablets sampled from pharmaceutical chemist and those sampled from patent medicine stores ($p>0.05$) (Table 1).

CONCLUSION

Quantitative drug assay was conducted at which the actual amount of active chloroquine in a tablet was determined. The low quality CQ preparations certainly contribute to an increase in drug pressure, which has been implicated as an important factor in the development of

Plasmodium falciparum resistance. Proper supervision of drug outlets coupled with well-coordinated inspection services enhance the chances of producing high quality pharmaceutical products in Nigeria.

ACKNOWLEDGEMENT

The authors are sincerely thankful to all that have contributed in the generation and processing of the data used in this study.

Conflict of Interest

There is no potential conflict of interest in this research work.

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Table 1: Quantitative chloroquine assay of samples from patent medicine stores and private pharmaceutical chemists

State	*Pharmaceutical chemists (PCH)*		*Patent medicine store (PMS)*		*Level of significance*	*Remark*
	CQ content (mg)	*CQ content (%)*	*CQ content (mg)*	*CQ content (%)*		
A	197.35 ± 61.50	78.94 ± 24.60	164.90 ± 65.75	65.96 ± 26.30	p>0.1 (NS)	P^+
B	194.93 ± 58.43	77.97 ± 23.37	215.38 ± 45.00	86.15 ± 18.00	p>0.05 (NS)	P^-
C	215.73 ± 51.30	86.29 ± 20.50	208.38 ± 57.00	83.35 ± 22.80	p>0.05 (NS)	P^+
D	239.02 ± 7.95	95.61 ± 3.18	226.02 ± 22.00	90.41 ± 8.80	p>0.01 (NS)	P^+

CQ = Chloroquine, P^+ = Depicts the difference in amounts of CQ content (in favour of PCH), P^- = Depicts the difference in amounts of CQ content (in favour of PMS)

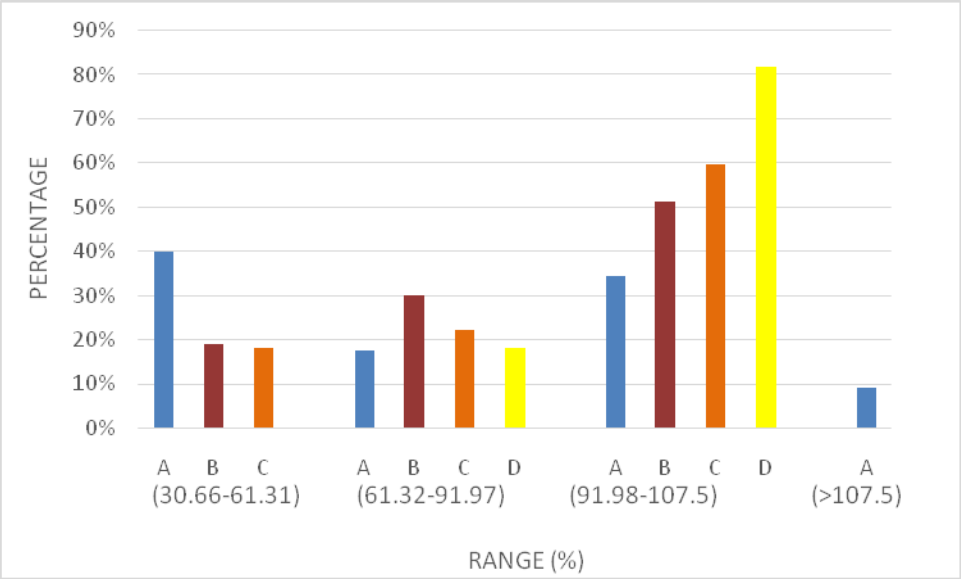

Figure 1: Non-aqueous assays of some brands of chloroquine tablets in study states (A, B, C and D = Study States)

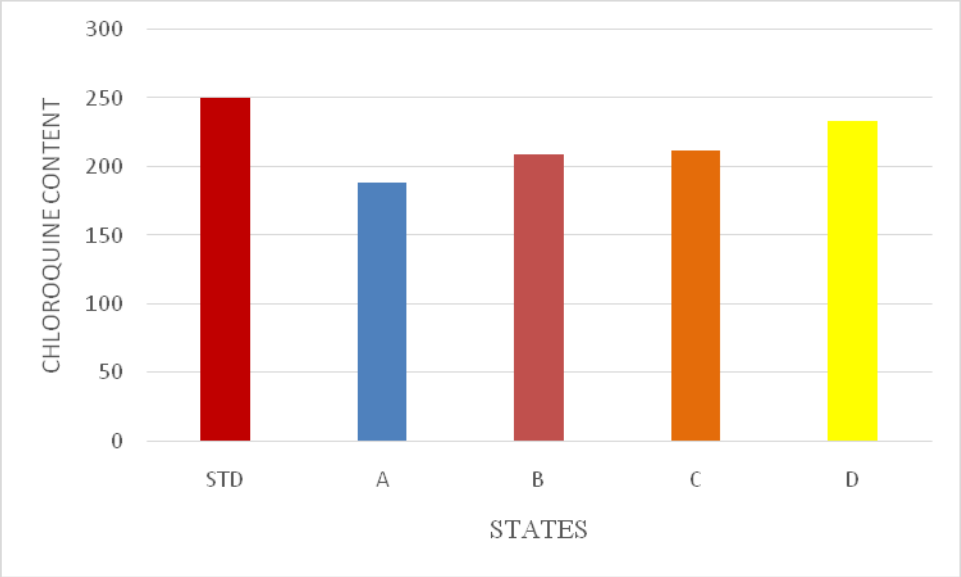

Figure 2: Mean active content of some brands of chloroquine tablet in study states (STD: Standard Chloroquine Content in Chloroquine Tablet)