Tropical Journal of Pharmaceutical Research May 2025; 24 (5): 591-597
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
https://dx.doi.org/10.4314/tjpr.v24i5.3

Original Research Article

Monitoring the quality of quinine injection in retail outlets in south-east Nigeria

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Sent for review: 15 March 2025 *Revised accepted: 17 May 2025*

Abstract

Purpose: *To determine the pharmaceutical quality of quinine injections sold in retail outlets in South-East Nigeria.*
Methods: *Eleven brands of 2 mL quinine injection (300 mg/mL) were examined for their quality and conformity to pharmacopeial standards. Various tests such as sterility, pH, clarity, extractable volume, test for identification and content uniformity test were performed as quality control measures. Content assay was determined by non-aqueous titration and UV spectrophotometry following the methods described in the British and United States Pharmacopoeias.*
Results: *All brands were sterile, without leakages and contained no particulate matter on white and black backgrounds. The extractable volumes from all the brands were slightly higher than expected, 2 mL. pH analysis showed that the injections have a pH not higher than 4.0. Only the brand, coded QH06, was outside the standard acceptable content of 90 – 110 % in both assay techniques. The non-aqueous titrimetric technique showed that only samples coded QH02, QH03, QH04 and QH08 contained 90 – 110 % of quinine, representing 36.4 %, while 72.7 % of the samples contained quinine within 90 – 110 % using UV spectrophotometric assay.*
Conclusion: *The study showed the presence of substandard quinine injection in Southeast Nigeria, which was characterized by suboptimal quinine strength. There is a need for regular post-marketing surveillance of available antimalarial injections in Nigeria to achieve therapeutic outcomes.*

Keywords: *Quinine, Non-aqueous titration, UV spectrophotometry, Post-marketing surveillance, Quality control*

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Nigeria has remained the epicenter of malaria infection in sub-Saharan Africa, accounting for 27 % of malaria cases and 31 % of malaria deaths globally despite being one of the 18 WHO African Region countries approved to receive support for the RTS, S/AS01 malaria vaccine rollout [1]. However, investments in quality chemotherapeutic interventions have continued to rise [1]. Antimalarials are the most commonly used medications, which are at risk of being

falsified in low- and middle-income countries (LMICs) [2]. A meta-analysis reported that 19.1 % of all antimalarials tested in LMICs were substandard or falsified [2]. Similarly, WHO reported that the incidence of counterfeit medicines was around 13.6 % in LMICs, and of these, antimalarials and antibiotics are the most commonly reported [3]. Most reports (42 %) come from the WHO African Region, 21 % from the WHO Region of the Americas, and 21 % from the WHO European Region. In Nigeria, nearly one in five antimalarials are substandard or falsified, which is approximately 19 % [4].

Separate reports by the African Fighting Malaria revealed that 35 % of antimalarials marketed in six African cities and in 21 sub-Saharan countries failed at least one critical quality control test or chemical analysis, and approximately, 20 % were falsified [5]. This high incidence of availability of substandard antimalarial drugs has made malaria management more challenging [6]. Counterfeiting of drugs is of grave concern to government and health authorities because it leads not only to increased morbidity and mortality but also to economic loss. According to WHO, around 1 million people die each year because of fake medications. Majority of them live in Africa, where it is estimated that 200,000 individuals pass away each year as a result of fraudulent antimalarial medications [7].

Furthermore, in many parts of the world, malaria parasites have become resistant to several antimalarial drugs, due in significant part to fake and sub-standard medications [5]. There is little resistance to quinine by malaria parasites and this has become the drug of choice in cerebral malaria as well as second line of treatment for uncomplicated malaria. Quinine has also shown significant therapeutic applications, singly or in combination with artemisinin derivatives, in multidrug-resistant cases, and pregnant women in the first trimester who have severe malaria or resistant falciparum malaria [8]. These factors have placed quinine in the spotlight and regular post-marketing surveillance will ensure that the right standard is delivered to consumers. Data on the quality, safety and efficacy of medicines, if properly collected, are vital for planning and implementing interventions to improve the quality of medicines.

Studies have provided some evidence for the presence of substandard antimalarial drugs in circulation in the Southwest, within the Southeast and South-South, Nigeria [9]. However, most of these surveys focused on oral formulations [7,10]. There is no study covering the whole of Southeast Nigeria that evaluated the pharmaceutical quality of quinine injection in drug retail outlets. A study conducted far back in 2009 in Anambra State (a part of Southeast Nigeria) indicated that as high as 46 % samples of quinine tablets were substandard [11]. It is, therefore, important to re-assess the level of exposure of patients to poor-quality quinine injections in a larger population and propose appropriate interventions.

EXPERIMENTAL

Materials

Glacial acetic acid, acetic anhydride, mercury (II) acetate, methanol, perchloric acid, sulfuric acid and hydrochloric acid were obtained from Sigma-Aldrich, Germany. Other reagents such as methylene blue, buffer solution, tryptone soy broth, quinine HCl RS (Alchem International, India), and crystal violet were of analytical grade. *Pseudomonas aeruginosa* was obtained from the Biotechnology Unit of Pharmaceutical Sciences, University of Nigeria, Nsukka.

Sampling location

Parenteral liquid quinine samples were collected from pharmacies and retail shops in two urban and two rural areas in each of the 5 Southeast States of Nigeria using a convenience sampling technique. The number of dosage units collected per sample was high enough to enable determination of triplicate quality assessment procedures. The study locations included randomly selected two rural areas each in Abia, Anambra, Ebonyi, Enugu and Imo States in Southeast Nigeria. The samples were procured randomly by researchers posing as normal customers.

Sampling protocol

Sample size was determined from the equation used for approximating the sample size of a finite population [12]. From the records of the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria, the total number of quinine injection products registered for use in Nigeria over the years was 21. With the prevalence of substandard and counterfeit antimalarial drugs reportedly about 19.1 %, in LMICs from previous studies, and the confidence level and margin of error were assumed to be 95 % and 10 %, respectively, the minimum sample size calculated was 16. However, total number of brands of quinine injection found in various pharmacies in Southeast Nigeria at the time of this study was 11 and they were all sampled for this study. One of the researchers, acting as a

buyer, purchased the different brands from wherever they could be found until 11 different brands were purchased.

After sample procurement in January 2023, the products and sampling information such as the exact date of purchase, place of purchase, manufacturer's address on the label, country of origin, brand name, product batch information, ampoule colour, pack size, manufacturing and expiry dates, labelled strength, and registration status were recorded from the product label (Table 1). The collected samples were stored in a refrigerator until they were analysed within 2 months after collection. All the brands manufactured in China, came in clear and slightly yellow ampoule colour with a pack size of 600 mg/2mL x 10.

Preliminary analytical procedure

The samples were subjected to analysis following the methods described in the monograph for quinine injection as outlined in the eighth edition of the United States Pharmacopoeia [13]. Each investigated sample was assigned a unique identification code ranging from QH01 to QH11 for provisional identification purposes.

Visual inspection for particulate matter

The clarity test was performed by visual inspection of the ampoules under white and black backgrounds. The ampoules from each quinine brand were gently agitated for 30 s and systematically placed against a black background, followed by a white background [13]. The white background was used to detect the presence of black particulate matter, while the black background was utilized to identify any white particulate contaminants.

Leakage test

Two ampoules were selected from each batch of quinine injection samples. Each sample was inverted, positioning the neck downwards, and vigorously flicked to assess for potential leakages, with observations duly recorded. A separate set of ampoules was immersed in a beaker containing methylene blue dye solution and subjected to heat for 2 h. After heating, the samples were removed and allowed to cool before examination for the presence of dye solution inside the ampoules, indicating potential breaches in seal integrity.

Determination of pH of injection

Digital pH meters were calibrated using pH buffer solutions at 4.0 and 7.0. After calibration, three ampoules from each pack of quinine injection samples were randomly selected and pH was measured. To ensure measurement accuracy, the pH meters were recalibrated with the buffer solution before each test.

Sterility test

Different brands of quinine dihydrochloride samples underwent sterility testing via direct inoculation, adhering to the European Pharmacopoeia guidelines [14]. For the determination of aerobic microbes, 0.5 mL of each sample was aseptically transferred into 4.5 mL of sterile tryptone soy broth and incubated at 35 °C for 14 days. *Pseudomonas aeruginosa* served as the positive control, while the broth without the test organism functioned as negative control. The broths were monitored daily for microbial growth, indicated by increased turbidity.

Table 1: Description of samples of quinine brands

Sample code	NAFDAC no	Batch no	Manufacture date	Expiry date
QH01	A4-1237	220926	09/2022	08/2025
QH02	04-7873	211051	10/2021	09/2024
QH03	04-9159	220868	08/2022	07/2025
QH04	A4-3727	210611	06/2021	06/2024
QH05	04-5360	EDQQI-007	07/2021	06/2024
QH06	04-6673	210709	07/2021	06/2024
QH07	A4-5870	211139	11/2021	10/2024
QH08	B4-7780	111210601	06/2021	06/2024
QH09	B4-6971	211207	12/2021	12/2014
QH10	-	210828	08/2021	08/2024
QH11	B4-6391	210419	04/2021	04/2024

QH- quinine sulphate; Dates were expressed as month/year; NAFDAC – National Agency for Food, Drug Administration and Control

Extractable volume of quinine injection

The volume of quinine injection extracted from a single ampoule using a 5 mL syringe was measured. For further analysis, 3 ampoules were randomly selected from a pack of each brand and their combined contents were transferred into a 10 mL measuring cylinder. The total volume was recorded. This procedure ensured an accurate assessment of the injectable volume from multiple ampoules.

Identity tests for quinine

(a) Colour test

The procedure involved shaking 0.25 mL of the sample with dilute sulfuric acid (1 in 350 mL) and stirring it. The solution was then placed in a dark room and exposed to 366 nm UV light. Following this, a few drops of hydrochloric acid were added, and colour changes were observed [15]. The presence of a strong blue fluorescence indicates the presence of quinine.

(b) UV-VIS-spectrophotometry

The monograph of International Pharmacopoeia [15] describes an identification test for quinine by employing UV-VIS spectrophotometry. From a stock solution of quinine HCl reference standard, 50 µg/mL solution was prepared in methanol. The solution was scanned from 200 to 400 nm using a UV-VIS spectrophotometer (Jenway Spectrophotometer) and the maximum wavelength of absorption was recorded. An ampoule from each brand was appropriately diluted with methanol, scanned with the UV-VIS spectrophotometer and its maximum wavelength of absorption was compared with the wavelength of maximum absorption.

Quantitative analysis of quinine

Non-aqueous titrimetric assay of quinine

The BP describes a non-aqueous method for the assay of quinine in its dosage forms [16]. A 1 mL aliquot of the sample was dissolved in a mixture consisting of 50 mL anhydrous acetic acid, 20 mL acetic anhydride, and 10 mL of mercury (II) acetate solution. One drop of crystal violet dissolved in glacial acetic acid was added to the mixture, swirled, and titrated with 0.1 M perchloric acid solution to endpoint (colour change: from purple to blue-green). The titre volume was recorded and triplicate determinations were made. The whole procedure was repeated with the other brands. The stoichiometry of the reaction is given below: 1 mL of 0.1 M perchloric acid is equivalent to 19.87 mg of quinine dihydrochloride.

(b) UV spectrophotometric assay of quinine

The calibration stock solution was prepared by weighing 10 mg of quinine RS into a 200 mL volumetric flask and dissolving it in 100 mL of methanol to create a 100 µg/mL solution. The mixture was sonicated for 5 min. Eight additional calibration standards (0.5 – 50 µg/mL) were prepared from the stock through serial dilution. For the sample assay, five ampoules from each sample were combined and vortex-mixed for 30 s. Subsequently, 1 mL was transferred into a 10 mL volumetric flask and diluted to volume with the diluent. This procedure was performed in triplicate. The final solution was mixed for 30 s and further diluted with the diluent to achieve the desired concentration for absorbance measurement at a wavelength of 350 nm.

Statistical analysis

Data was analyzed using GraphPad version 5 (GraphPad Software, San Diego, CA, USA) software. Results were expressed in mean ± standard deviation (SD).

RESULTS

Preliminary description of quinine injections

All the brands studied were obtained in 1 x 10 ampoule packs with claims of 600 mg of quinine dihydrochloride in a 2-mL volume strength. Eleven brands of quinine formulations were found within the study region, representing 52.47 % of quinine injection brands registered by NAFDAC for use in Nigeria. All the products were imported from China (Table 1).

Physicochemical inspection

The visual inspection showed that the quinine injections contained no visible particulate matter on white and black backgrounds. There was no disclosure of the excipients used in the formulation. Also, the extractable volume was slightly higher than the expected extracted volume (2 mL). A total of 8 (72.7 %) products showed an extractable volume 3.5 % higher than expected, while 1 product (9.1 %) each had an extractable volume of 6.65, 10 and 16.65 % higher, respectively. The leakage and sterility tests showed that none of the ampoules had leakage and also, they were all sterile and clear. The pH analysis showed that the injections have pH not higher than 4.0.

Table 2: Physicochemical inspection of quinine injection brands

Sample code	V_{ex}	pH
QH01	2.067±0.058	3.2±0.1
QH02	2.067±0.058	4.0±0.3
QH03	2.067±0.173	3.0±0.1
QH04	2.200±0.058	3.1±0.1
QH05	2.067±0.058	3.4±0.2
QH06	2.067±0.058	3.0±0.1
QH07	2.067±0.058	3.0±0.1
QH08	2.333±0.289	3.8±0.4
QH09	2.067±0.058	2.8±0.1
QH10	2.067±0.058	3.1±0.1
QH11	2.133±0.116	3.3±0.1

Extractable volume (V_{ex}) values were expressed as mean ± SD

Quinine HCl or sulphate

Quinine content of the products was identified by colour reaction as specified in various Pharmacopoeias [14-16]. A 0.005 M solution of quinine in sulfuric acid (1 in 350 mL) displayed blue fluorescence UV light at 360 nm, which disappears with the addition of a drop of hydrochloric acid. All the products produced a blue colouration to the sulfuric acid test, which disappeared in hydrochloric acid, indicating the presence of quinine in all the brands.

Quantification of quinine

Non-aqueous titrimetric assay of the quinine content of the product showed variable composition. One product (QH04) contained > 100 % of quinine; 3 showed > 90 %, 3 contained between 70 – 90 %, while one product (QH10) contained < 40 % (Table 3).

Table 3: Assay of quinine content by non-aqueous titration

Sample code	Average Titre (mL)	Quinine (mg)	Quinine (%)
QH01	13.0±0.7	258.31±12.67	86.10
QH02	14.6±1.3	290.10±14.63	96.70
QH03	14.0±0.8	278.18±9.25	92.72
QH04	16.0±0.3	317.92±9.65	105.97
QH05	10.0±1.0	198.70±10.84	66.23
QH06	12.0±0.3	238.44±9.45	79.48
QH07	12.0±0.6	238.44±8.44	79.48
QH08	14.0±0.5	278.18±10.23	92.72
QH09	9.0±0.6	178.83±9.30	59.61
QH10	6.0±0.6	119.02±11.50	39.67
QH11	8.0±0.2	158.96±6.47	53.00

UV spectrophotometry of quinine

Calibration curve for the spectrophotometric assay of quinine at 275 nm showed a regression curve with a significant deviation from zero ($p < 0.0001$), slope of 0.01969 ± 0.0004938, y-intercept of -1.452 to 0.1799 ($F = 1590$, $DFn = 1.000$, $DFd = 6.000$) and R^2 of 0.9962. Assay of quinine in the products by UV spectrophotometric method showed variable composition (Figure 1). Eight of the eleven samples (72.7 %) contained 90 – 110 % quinine while two samples (QH02 and QH04) contained significantly lower quinine concentrations.

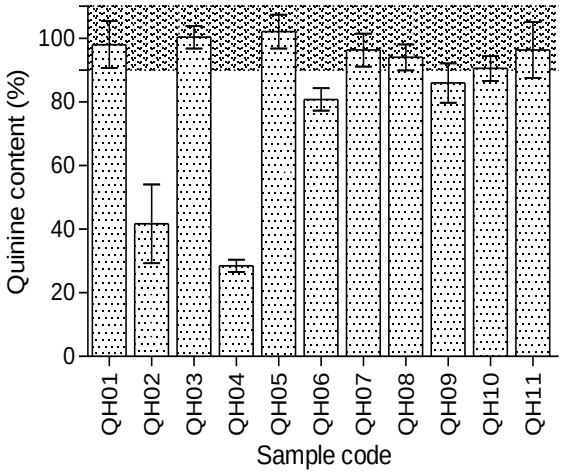

Figure 1: Assay of quinine content by UV spectrophotometry (range of acceptable limit of quinine content of 90 – 110 % as specified in the USP 2019 is the shaded upper part)

DISCUSSION

Quality assurance of quinine injection involves a comprehensive check to ensure that the medication is safe, efficacious and reliable. Assessment of product information to confirm that it meets quality standards, identity and purity tests, compliance to good manufacturing practices, sterility, stability tests, packaging and labelling accuracy as well as regulatory approvals are necessary to ensure safe and effective medication for patients who rely on them in the treatment of malaria [13]. Quinine injections are parenteral products injected into body fluids, and bypass protective mechanism. As a result, they must comply strictly with monograph specifications. All parenteral preparations must be sterile, free from particulate matter, must be isotonic with the body fluid, and the filled volume must be more than the stated volume to ensure dosage accuracy. The container must be compatible with the active pharmaceutical ingredients and the excipients and must be sealed to avoid leakage and contamination from the environment. All pharmaceutical products must contain the stated amount of active pharmaceutical ingredients on the label. It is important to carry out quality control and validation of pharmaceutical products during and after production to ensure compliance with monograph specifications which translates

to safety and pharmaceutical quality of the drug product [15,16].

Apart from the clarity, leakage and sterility tests which showed 100 % compliance with monograph specifications [13], there were several inconsistencies among the brands studied and the tests carried out. The leakage test is a formulation parameter that is normally performed to detect incompletely sealed ampoules by the application of pressure in a vacuum. It is done to ensure that the ampoules are completely sealed. From the result of the test, all the brands passed the leakage test. Clarity test is a necessary test for parenteral as particulate matter is not meant to be found in any parenteral product, because it may block body capillaries [17]. To this effect, every ampoule must be inspected over a white and black background and must be found to be clear to the human eye. The result showed that all the samples examined were free from particulate matter. A sterility test is an indispensable test as a microbe-contaminated product may cause septicaemia or other fatalities. It is performed to ensure that no viable microbe is found in the parenteral product since parenteral products bypass the body's defensive barriers and mechanisms. The test results showed that the eleven brands of quinine injections passed the sterility test [17].

Conformity with extractable volumes of injection is necessary to ensure that accurate dosing is obtained while administering quinine. The study did not record any extractable volume lower than 2 mL suggesting an adequate quantity that would ensure proper dosing and an effective therapeutic outcome. It has been reported that inconsistent doses arising from administering lower extractable volumes of antimalarial drugs could result in the emergence of quinine-resistant strains of plasmodium in the regions where quinine is relied on for the treatment of uncomplicated and cerebral malaria [18]. According to the monograph, the pH of injectable solutions must be between 3.0 and 5.0. All samples passed the pH test except sample QH09 which is slightly below the acceptable range (pH of 2.8).

Identification tests for quinine were done using qualitative colour reaction and UV spectrophotometry. The typical colour reactions of a strong blue fluorescence confirmed the presence of quinine in all the samples. Also, the UV spectra of the diluted solutions of the various brands had same wavelength of maximum absorption. According to the US Pharmacopeia [13], the acceptance criteria for quinine injections must be between 90 – 110 %. In the non-aqueous titration assay technique, only 4 samples QH02, QH03, QH04 and QH08 contained quinine that is within this specification. In the UV spectrophotometric assay, only samples QH02, QH04, and QH06 did not contain up to 90 % quinine and no sample contained up to the upper limit of 110 %. This corresponds to 27.3 % of sampled drugs found to be sub-standard in content uniformity test. The non-compliance of some brands of quinine injection to the recommended official standard of not less than 90 % and not more than 110 % of quinine stated on the label may be attributed to possible photodegradation of quinine [19]. A pairwise comparison of the two techniques adopted in this study showed that the results from the non-aqueous titration did not tally with those of UV spectrophotometry. For instance, in the titration method, QH02 and QH04 had quinine in the acceptable range and failed the content test with the spectrophotometric method. Failure of only three brands in the UV spectrophotometric assay compared with seven brands in the titrimetric method out of the eleven brands sampled supported the wider applicability of UV spectrophotometric technique due to its high sensitivity and precision, non-destructive, quick analysis and its suitability for detecting low concentration of quinine.

The major potential challenges of suboptimal strengths of antimalarial injections include the higher risk of reduced efficacy, treatment failure, delayed parasite clearance time, more recrudescence, and the emergence of resistance which becomes more crucial in the treatment of malaria, particularly when quinine is considered for severe malaria cases or is the only available or affordable option [18]. Results of this study showed that none of the quinine injection brands were counterfeit since they all contained the active pharmaceutical ingredient (API). However, they conform with several earlier reports on the prevalence of substandard medicines, especially antimalarials in LMIC, including Nigeria [2,4,6,7,10].

CONCLUSION

The study shows that none of the quinine injection brands is counterfeit since they all contained the API. However, there is still availability of suboptimal quinine strength in Southeast Nigeria. There is a need to continue with regular post-marketing surveillance of available antimalaria injections in Nigeria to ensure sustained, and efficient therapeutic outcomes.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

None required.

Use of Artificial intelligence/Large language models

We also declare that we did not use generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors approved the final version of the manuscript.

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