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Influence of a Nigerian honey on CYP3A4 biotransformation of quinine in healthy volunteers

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Abstract

What is known and objectives—Some studies, howbeit with conflicting reports have suggested that consumption of honey has a potential to modulate drug metabolising enzymes which may result in a honey - drug interaction. Numerous studies have established that honey varies in composition, influenced by the dominant floral, processing and environmental factors. Thus, variation in honey composition may be a contributing factor to the controversial results obtained. No previous drug interaction study has been done with any honey from Africa. CYP 3A4 is an important enzyme in drug metabolism studies as it is involved in the metabolism of over 50 % of drugs in clinical use and quinine remains very relevant in malaria treatment in the tropics, we therefore determined whether there is potential drug interaction between a Nigeria honey and quinine, a drug whose metabolism to 3 –hydroxyquinine is mediated majorly by CYP3A4.

Methods—In a three phase randomized cross-over study with a wash out period of two weeks between each treatment phase, ten (10) healthy volunteers received quinine sulphate tablet (600 mg single dose) alone (phase 1) or after administration of 10 ml of honey (Phase 2) and 20 ml of honey (Phase 3) twice daily for seven (7) days. Blood samples were collected at the 16th hour post quinine administration in each phase and quinine and its major metabolite, 3-hydroxyquinine were analyzed using a validated HPLC method.

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Results—After scheduled doses of honey, the mean metabolic ratios of quinine (3-hydroxyquinine/quinine) increased by 24.4 % (with 10 ml of honey) and reduced by 23.9 % (with 20 ml of honey) when compared to baseline. These magnitudes of alteration in the mean metabolic ratios were not significant ($p > 0.05$; Friedman-test). The geometric mean (95 % CI) for the metabolic ratio of quinine before and after honey intake at the two dose levels studied were 0.82 (0.54, 1.23) and 1.29 (0.96, 1.72) respectively and were also not significant ($P = 0.296$ and 0.081 respectively; student t-test).

What is new and conclusion—This is a pioneer study on the effect of Nigeria/Africa honey on quinine metabolism. The findings indicated that low and high doses of honey did not significantly affect metabolism of quinine to 3-hydroxyquinine. This suggest that CYP3A4 activity is not significantly altered following low or high dose of honey, since CYP3A4 has been reported to be responsible for the conversion of quinine to 3-hydroxyquinine. In conclusion, the outcome of this study suggests that there may be no potential significant metabolic interaction between Nigeria honey and quinine administration.

Keywords

Quinine; Nigeria-Honey; CYP3A4; Herb-drug interaction

INTRODUCTION

Several lines of evidence indicate that an increase in concurrent consumption of medicinal herbs or dietary supplements with conventional therapeutic agents increases the possibility of drug-food/herb interaction with consequent therapeutic outcomes[1, 2]. Since herbal dietary supplements or products are not regulated like drugs, their compositions, doses and frequencies of use are more variable and may deliver compounds with the potential to modulate drug metabolising enzymes.[3] Honey is a common household nutritional supplement of plant-origin with variable bioactive components from the nectars of various plants[4], with no restriction on the amount taken. Climate and environmental conditions have been shown to alter the composition of plant. For instance, the fruit of grape fruit tree exposed to freezing temperature has been reported to produce more naringin in response to environmental stress[5]. Similarly, numerous studies have reported that floral sources, seasonal and environmental factors in different geographical regions affect the type and amount of components, especially the phenolic constituents present in honey [4, 6–11] leading to a variation in honey constituents. Honey components include sugar, and flavonoids (quercetin, kaemferol, and luteolin) which have been reported to alter activities of drug metabolising enzymes[7–9]. CYP3A is an important enzyme in drug metabolism because it is involved in the metabolism of over 50 % of drugs in clinical use[15, 16]. Existing studies that evaluated the effect of honey from various geographical regions on the activities of drug metabolizing enzymes in rats and humans revealed conflicting results. Specifically, results from such previous studies showed that honey from India significantly induced CYP3A in animal models[17–19] and man[20]. On the contrary, studies by Fetzner *et al*[21], suggested that honey from Germany did not significantly modulate CYP3A activity in human.

Following an exhaustive literature search, no study was found to have assessed the effect of any honey from Nigeria or any African region on drug metabolising enzyme. A survey

(unpublished) we conducted prior to the commencement of this study revealed that honey is largely and commonly consumed both as sweetener and for its medicinal benefit. Since geographical location has been reported to influence the composition of honey, and there are no examples of drug interaction studies between Nigeria honey from tropical climate and any drug, we therefore evaluated the effect of honey from Nigeria on CYP3A4 mediated metabolism of quinine. Several lines of evidence indicate that the metabolism of quinine to 3-hydroxyquinine is mediated by CYP3A[22–26.] Although the use of quinine as a drug to probe the activity of CPY3A4 has not been fully resolved, recent study [29], demonstrated that quinine metabolic ratio has been found to be comparable to midazolam clearance in plasma as a measure of CYP3A-activity. Midazolam has been established as a validated and recommended probe drug for CYP3A activity[30]. Quinine used as a substrate marker for CYP3A4 in this study has continued to find use in the treatment of severe and complicated malaria in Sub-Sahara Africa where malaria is endemic[31] coupled with honey being a highly popular food supplement in Africa. Hence assessment of the effect of honey on CYP3A4 mediated quinine metabolism may suggest the effect of honey-quinine interaction on the outcome of quinine therapy. The metabolic ratio of 16th hour plasma sample of quinine[22, 23, 27, 28] was used to assess the modulating effect of multiple dose honey intake on CYP3A mediated metabolism of quinine to 3-hydroxyquinine in healthy volunteers.

METHODS

Subjects

Ethical approval was obtained from Obafemi Awolowo University Teaching Hospital Complex Research Ethics Board and Safety Committee. Ten healthy subjects (range; mean ± SD: age, 20–28 years; 23.5 ± 3.0 and weight, 51–77 kg; 64.4 ± 7.9 kg) who gave written informed consent were recruited for this study. All subjects were declared healthy and fit for the study following assessment by a medical doctor, laboratory and clinical investigations. Volunteers were excluded from the study if on alcohol, on tobacco, pregnant, breast feeding, suffering from chronic disease, on quinine therapy or with known hypersensitivity reaction to quinine or similar agent. Subjects were told not to take any herbal dietary supplements, fruits juices, honey and quinine one week prior to and during the study.

Honey sample

Honey sample used in this study was purchased from a bee keeper in Ewu, a town located in the Western region of Nigeria. The floral (presumably what the bees fed on) within about 5 km distance from the beehives were *Chromolaena odorata* (Siam weed), *Mangifera indica* (Mango), *Tectoa grandis* (Teak), *Elaeis guineensis* (Palm) and *Morinda lucida* (Moringa) tree. Prior to the commencement of this study, a survey (Unpublished) was conducted and the result showed that people who used honey regularly took between 20 – 40 ml of honey per time. This was the rationale for the amount of honey used in this study

Study Design

The study was a randomized open label, three-phase crossover pharmacokinetic design, with each subject being his own control in order to minimize inter-individual variation in the ten healthy subjects who participated in the study. A wash-out period of two weeks was allowed

between each study phase. In phase 1, each of the ten healthy volunteers after an overnight fast, received a single oral dose of 600 mg of quinine sulphate tablet (Maderich Ltd, Surrey, England). Blood samples (5 ml) were withdrawn by venepuncture from the forearm before and at the 16th hour post drug administration into EDTA tubes, centrifuged (3000 g for 10 mins) immediately and the resulting plasma was stored at −20º C until analysis. In subsequent phases, each subject ingested honey (10 ml in phase 2 and 20 ml in phase 3) twice daily for seven days and thereafter received quinine as given in phase 1. Blood samples were again collected and analyzed for quinine and its metabolite, 3-hydroxyquinine.

Analytical methods

The concentrations of quinine and its metabolite, 3-hydroxyquinne in plasma were determined using a high performance liquid chromatographic method described by Babalola *et al*[32], but with slight modification. Before extraction of drug and metabolite, 3.0 μg/ml of primaquine (Internal standard) was spiked into 1.0 ml of plasma samples. Sample extraction involved protein precipitation with 0.64 ml perchloric acid (70 % w/w, density 1.664 g/ml), followed by basification with 1ml of 5 M NaOH and subsequent extraction using 4ml of diethylether and back extraction into 100 μl of 0.1 M HCl. 50 μl of the aqueous layer was loaded onto the HPLC 20 μl injector with the excess flowing out of the injector outlet tube. The high performance liquid chromatographic system used consisted of an Agilent 1200 series HPLC system (Agilent Technologies, Santa Clara, Califonia, USA) fitted with an isocratic pump (model G1341A), a UV detector (model G1341B) and manual injector valve with a 20 μl sample loop. The chromatographic separation was achieved with an Eclipse XDB-C18 reverse phase HPLC column (150 x 4.6 mm internal diameter) with a 5-μm particle size (Agilent USA). The mobile phase (pH = 2.6) consisting of methanol, acetonitrile and 0.02 M KH_2PO_4 buffer (15:15: 70) containing 0.64 ml of perchloric acid (70% w/w, density 1.664 g/ml) was pumped at a flow rate of 1.6 ml/min. The column eluent was monitored at a wavelength of 254 nm. LC3D Chemstation software was used for data acquisition. Calibration procedure used has been previously reported[32]. The elution time for metabolite, drug and internal standard was less than 10 min. The Standard curve was linear over the concentrations range (0.25 – 4.0 μg/ml) for both quinine and metabolite. The coefficient of determination was 0.999 and 0.9995; limit of quantitation was 0.37μg/ml and 0.5μg/ml for quinine and 3- hydroxyquinine respectively. At concentrations of 0.25 and 4.0 μg/ml, the intra-day and inter-day coefficient of variation was less than 4 %, recovery was greater than 93.9 % for quinine and 73.4 % for 3-hydroxyquinine. The accuracy ranged between 93.1 % and 105.9 % for both drug and metabolite.

Data and Statistical Analysis

The Metabolic ratio (MR) of quinine calculated as the molar concentration ratio of 3-hydroxyquinine (metabolite) and quinine (drug) in the 16th hour plasma collection[17, 22,] was used to estimate the effect of honey on the metabolism of quinine.

$$\text{Metabolic ratio} = \frac{\text{plasma concentration of } 3-\text{hydroxyquinine at the } 16^{\text{th}} \text{ hour}}{\text{Plasma concentration of quinine at the } 16^{\text{th}} \text{ hour}}$$

Statistical analysis

Data was expressed as mean ± SD and $p < 0.05$ was considered statistically significant for all procedure. Friedman test was used to determine significant difference across the mean metabolic ratio of 3-hydroxyquinine/quinine of the ten healthy volunteers obtained upon administration of quinine alone (baseline: phase 1); quinine plus 10 ml of honey twice daily for seven days (Phase 2); and quinine plus honey 20 ml of honey twice daily for seven days (Phase 3). Additionally, the individual raw data was log transformed and the mean difference between the metabolic ratio obtained with quinine alone and quinine in the presence of honey at the respective honey dose level studied was calculated ($\log MR_{\text{quinine alone}} - \log MR_{\text{quinine and honey}}$) and presented with the antilog. The corresponding 95% confidence intervals for the MR were calculated from the antilog of the mean. Student t- test was used to determine any statistically significant differences in the mean MR of quinine at baseline versus the respective doses of honey studied.

RESULTS

Overall quinine given alone or with honey was well tolerated as only three out of the ten volunteers complained of side effects as nausea, headache and dizziness. These were mild and transient and all enrolled subjects completed the study. Figure 1 presents the mean metabolic ratio of 3-hydroxyquinine to quinine for the ten volunteers who received quinine (600 mg) alone and with multiple adminstration of 10 ml or 20 ml honey twice daily for seven days. Table 1 presents the summary of the metabolic ratio (mean ± SD) for quinine at baseline and with ingestion of honey. As shown in the table, the mean metabolic ratio of quinine at baseline (0.64 ± 0.23), or with 10 ml twice daily (0.80 ± 0.36) or 20 ml twice daily of honey (0.49 ± 0.16) was not significantly different ($p > 0.05$). The magnitude of alteration in the mean metabolic ratio of quinine in the presence of 10 ml of honey taken twice daily increased by 24.4% but reduced by 23.8 % with 20 ml twice daily dose of honey (Table 1). The geometric mean [95 % Confidence Interval (CI)] for the metabolic ratio of quinine before and after honey intake at the two dose levels studied were 0.82(0.54, 1.23) with 10ml of honey; and 1.29 (0.96, 1.72) for 20 ml of honey (Table 2). Statistical analysis of the geometric means gave $P = 0.296$ and $P = 0.081$ respectively (Table 2), showing that the metabolic ratio of quinine in the presence of the lower dose or higher dose of honey compared to baseline were comparable (Student t-test; $p > 0.05$).

DISCUSSION

We investigated the potential effect of a Nigerian honey on the metabolism of quinine, a CYP3A substrate. To the best of our knowledge, this is the first study that evaluates the effect of any honey from Nigeria or Africa on the disposition of any drug. Our results (Tables 1 and 2) revealed that multiple doses of honey did not significantly alter the 16^{th} hour mean metabolic ratio of quinine (3-hydroxyquinine/quinine) when compared to baseline. Previous studies have established that the metabolism of quinine to 3-hydroxyquinine is mediated by CYP3A and also, the metabolic ratio in a single plasma or urine sample collected 16 hours post quinine administration can serve as a stable measure of the hepatic activity of CYP3A mediated formation of 3-hydroxyquinine in humans[22–27].

Even though the use of quinine has not yet been recommended or recognized as a CYP3A4 probe[33], a recent study evaluated a single metabolic ratio of quinine and validated CYP3A4 probes, midazolam and 4β-hydroxycholesterol and found it to be comparable for determining CYP3A-induction[30]. In a previous study, Wanwimolruk *et al*[23] suggested that quinine may serve as an *in vivo* probe to assess within-subject inhibition of liver CYP3A4 activity. However, just as for other recommended CYP3A probe, further studies may be needed to further investigate quinine as a potential and validated CYP3A4 probe during various conditions. For this reason, we designed a within subject study where the metabolic ratio of 16th hour plasma sample of quinine was used to assess the modulating effect of honey on CYP3A mediated metabolism of quinine to 3-hydroxyquinine in healthy volunteers.

Even though the results of our study suggest that honey did not significantly modulate CYP3A-mediated metabolism in healthy human volunteers as evidenced from the metabolic ratio of 3-hydroxyquinine/quinine observed, the mean metabolic ratio of quinine compared to baseline increased by 24.4 % with lower dose of honey but reduced by 23.9 % when the amount of honey taken by the volunteers was doubled. This result indicates that honey produced a dose dependent biphasic effect on the pattern of quinine metabolism with a lower dose of honey suggestive of stimulation (Fig. 1), and higher dose indicative of inhibition (Fig. 2) of CYP3A4 activity. This observation is consistent with the findings of Kang *et al*[34] where quercetin (one of the flavonoids found in honey) had a concentration dependent effect, where lower doses stimulated and higher doses inhibited CYP1A2 activity in a system expressing human CYP1A2. A fuller dose-response evaluation between quinine and honey using a larger population and an extensive sampling procedure seems necessary to confirm this possibility of a dose dependent effect of honey on quinine or as the case may be, other CYP substrates.

It is noteworthy that the few drug-honey interaction studies reported in literature observed different effects of honey on CYP3A. For example, in a study were 10 ml of an Indian-honey was used twice daily for seven days in healthy volunteers, the excretion of endogenous 6-betahydroxycortisol, a CYP3A marker was significantly increased[20], while in a more recent study with midazolam as the marker; authors reported that German-honey at a dose of 14.3 ml for 10 days did not significantly alter the activities of CYP3A[21]. Although, we used a different CYP3A substrate and a much higher amount of Nigeria-honey, the result of our finding is consistent with the more recent study[21]. This present study was premised on the knowledge that since honey is not a standardized substance and its composition varies, one might expect to observe differences in the result of drug interaction studies conducted with honey from different climatic region. This study had some limitations in that we did not analyse the flavonoids composition of the honey used in this present study. Previous honey drug interaction studies also had this limitation except the recent study by Fetzner *et al*[21].

In conclusion, the results of this study indicate that multiple administration of honey in the amount used in this study showed a dose dependent biphasic effects on quinine metabolism though honey did not significantly alter quinine hepatic CYP3A biotransformation of

quinine to its major metabolite, 3-hydroxyquinine. This indicates that ingestion of honey with quinine, may not elicit any serious drug-nutrient metabolic interaction.

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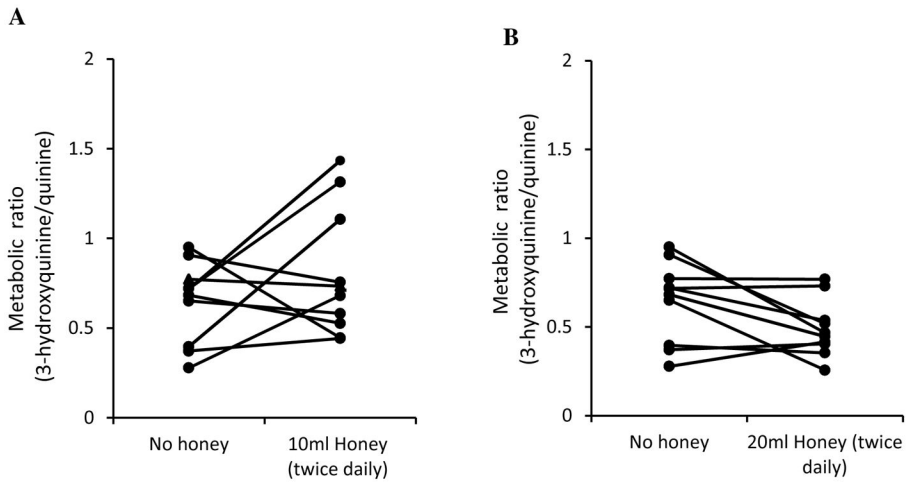

Fig. 1.

Metabolic ratio of 3-hydroxyquinine and quinine following oral administration of 600 mg quinine sulphate tablet to ten healthy volunteers before and after each volunteer received 10mls (A) or 20mls (B) of honey twice daily for 7 days (n = 10)

Table 1

Summary of 16th hour mean metabolic ratio of quinine (3-hydroxyquinine/quinine) following oral administration of 600 mg of quinine sulphate tablets alone or after honey intake for seven days. (n=10)

Treatment	Mean Metabolic Ratio (3-hydroxyquinine/ quinine)	% change in Mean Metabolic ratio	P-value
Quinine alone (baseline)	0.64 ± 0.23		
Quinine + Honey (10ml twice daily)	0.80 ± 0.36	↑24.4 %	0.15
Quinine + Honey (20ml twice daily)	0.49 ± 0.16	↓23.9 %	

(Friedman- test; Statistically significant P<0.05)

Table 2

Log-transformed mean metabolic ratio of quinine (3-hydroxyquinine/quinine) following oral administration of 600 mg of quinine sulphate tablets alone or after honey intake.

Treatment	Mean Metabolic Ratio (3-hydroxyquinine$_{log}$ – quinine$_{log}$)	95% CI	P value
Quinine alone and Quinine + Honey (10ml twice daily)	0.82	0.54, 1.23	0.296
Quinine alone and Quinine + Honey (20ml twice daily)	1.29	0.96, 1.72	0.081

CI, Confidence interval.

Statistically significant P <0.05; Paired t- test calculated for log-transformed MR of quinine (with and without honey).