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Effect of dehusked *Garcinia kola* seed on the overall pharmacokinetics of quinine in healthy Nigerian volunteers

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Abstract

We investigated the effect of concurrent ingestion of *Garcinia kola* seed on the pharmacokinetics of quinine. In a randomized crossover study, 24 healthy Nigerian volunteers were assigned into two groups (A and B; n = 12 per group) on the basis of *G. kola* dose orally ingested. Each subject received 600mg quinine sulphate before and after ingesting 12.5g of *G. kola* once daily for seven days (Group A) or 12.5g twice daily for six days and once on the seventh day (Group B). Blood samples were collected and analyzed for plasma quinine and its metabolite, (3-hydroxyquinine) using a validated HPLC method. Concurrent administration of quinine with *G. kola* reduced quinine $t_{\max}$ by 48% (group A), mean $C_{\max}$ by 19% and 26% in groups A and B, and slight reduction in mean $AUC_{0-\infty}$ of quinine in both groups. 3-hydroxyquinine $C_{\max}$ also reduced by 29% and 32%; $AUC_{0-\infty}$ by 13% and 9% respectively. The point estimates of the T/R ratio of the geometric means for all $C_{\max}$ obtained and only the $AUC_{0-\infty}$ at a higher dose of *G. kola* were outside the 80–125% bioequivalence range. In conclusion, an herb-drug interaction was noted with concurrent quinine and *G. kola* administration.

Keywords

Garcinia kola; Quinine; 3-Hydroxyquinine; Pharmacokinetics; Drug-herb interactions

Use of natural products such as herbs and supplements for health maintenance has become very popular, raising the potential for interactions when administered in combination with

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Conflict of Interest

The authors listed in this manuscript have no conflict of interest or competing interest with respect to the outcome of the study.

prescription drugs. [1, 2] *Garcinia kola* seed commonly called bitter kola is a highly valued ingredient in African ethno-medicine and is used in the management and treatment of several ailments such as coughs, cold, voice hoarseness, aphrodisiac, and liver diseases. [3, 4] It is also relevant in traditional medicine, cultural and social ceremonies in many parts of West and Central Africa. [4, 5] The seed is often ingested as a dietary supplement, and some proprietary dietary supplements of *G. kola* seed or its extract, alone or in combination with other phytochemicals are now used in the management of several clinical conditions. [4] Studies on phytochemical analysis of *G. kola* seeds [6–11] reveal benzophenones, xanthenes, alkaloids, phenols, tannins and saponins, kolaviron a biflavonoid complex, and metallic ions such as aluminum, magnesium, calcium and copper as major chemical components of *G. kola*.

The seeds or its extracts have been reported to modulate the pharmacokinetics of some drugs in humans and alter the activities of cytochrome P450 *in vitro* [12–16]. Assessment of *in vitro* CYP inhibition of natural products is important for predicting product-drug interactions if these products are taken concomitantly. In this context, herb-drug interaction studies are necessary to determine the absence or presence of such *in vivo* drug interactions. [17] The continued relevance of quinine in malaria therapy in sub-Saharan Africa [18] raises the possibility of its concomitant use with other natural therapeutic agents. The customary use of *G. kola* in certain regions in Western African countries coupled with the prevalence of malaria in this geographical region suggest that there is a possibility of the concurrent use *G. kola* and quinine. This may result in a potential herb-drug interaction with serious consequences, such as therapeutic failure or toxicity. Such interaction could occur at any stage of the pharmacokinetic process. [19] Indeed, quinine has been demonstrated both *in vivo* and *in vitro* as a substrate for CYP3A enzyme [20–24]. This enzyme is responsible for the formation of 3-hydroxyquinine, a major metabolite of quinine [21, 22] and the metabolism of at least 50 % of clinically administered drugs [25] making it an important enzyme.

Despite the extensive consumption and use of *G. kola* in folkloric remedies for the treatment of various diseases, [3–4, 10] the interactions of *G. kola*, with prescription medications has not been fully investigated. In the current study, we analyzed the potential interaction between *G. kola* ingestion and quinine disposition in healthy volunteers. Our analysis determined whether the concurrent ingestion of *G. kola* with oral quinine administration elicited a pharmacokinetic interaction. Since metabolic ratio can be used as a measure of enzyme activity, [26] we also determined activities of CYP3A in healthy humans using the metabolic ratio of 3-hydroxyquinine/quinine in plasma as a measure of assessment of the metabolism of quinine to 3-hydroxyquinine by CYP3A. [22]

METHODS

Subjects

Before the commencement of the studies, ethical approval was obtained from the Obafemi Awolowo University Teaching Hospital Complex Research Ethics Board and Safety Committee and conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. We used the amount of *G. kola* to be taken to randomly divide

twenty four healthy Nigeria men and women into two groups of twelve volunteers. Volunteers recruited were non smokers and were not on any other medication or continuous medication for at least two weeks prior to commencement of the study. Pregnancy, breastfeeding, histories of hypersensitivity to quinine or similar agents, or adverse side effects from taking *G. kola* seeds were also used as exclusion criteria for the study. Participants were certified healthy by a physician based on medical history, clinical examination, and laboratory tests and they gave their written informed consent to comply with the study protocol.

Study design and *G. kola* and quinine administration

A two phase study was employed in two separate studies. Each phase of the study was a randomized, open label, two-step pharmacokinetic cross over design with a wash out period of two weeks between treatments. Participants were randomly divided into two groups (A and B) of 12 persons each. In the first phase, after an overnight fast, each subject in the respective groups received a single oral dose of 600 mg quinine sulphate tablets (Maderich Ltd, Surrey, England). The second phase of the study commenced a week after drug administration. *Garcinia kola* seeds used in these studies were obtained locally in Ile – Ife (South-western part of Nigeria) and were certified in the herbarium of the Department of Pharmacognosy, Obafemi Awolowo University, Nigeria. Participants in group A ingested 12.5 g of dehusked *G. kola* seed once daily for seven days while those in group B received 12.5 g of dehusked *G. kola* seeds twice daily for six days and once on day 7. The choice of ingesting kola twice daily was to evaluate if a higher dose of *G. kola* ingestion is associated with further changes on quinine kinetics. Doses of *G. kola* in this study were chosen based on the consumption pattern from a survey conducted prior to this present study and reports from doses employed in previous studies, both in rats and in man. [9, 27–28] Prolonged administration of *G. kola* ensured that a possible induction of enzyme activity by *G. kola* could be evaluated since it is known that enzyme inhibition may occur with the first dose of the inhibitor [29–30], while an inducer can cause an increase in enzyme activity over time usually at a relatively higher dose of the inducing agent. [31] During the seventh day of bitter kola administration, coinciding with the end of the wash out period, each participant after an overnight fast received bitter kola concomitantly with the administration of a single oral dose of 600 mg quinine sulphate tablets.

Tolerability assessments included physical examinations, supine blood pressure, pulse rate and adverse-events (AE) monitoring using investigators' questionnaires and subjects' spontaneous reports.

Sample collection

Venous blood samples (5ml) was collected into heparinised tubes at time zero (just before the administration of quinine sulphate tablets)) and at 1, 2, 3,4, 6, 8, 12, 24, 36 and 48 h after each participant received quinine alone or concurrently with the scheduled dose of *G. kola*. For pharmacokinetic assay, the blood sample was centrifuged (3000 g for 10 mins) and the resulting plasma was stored at –20 °C until the time of drug analysis.

Drug Analysis

A slight modification of an earlier reported HPLC method [32] was used to assay for quinine and its major metabolite, 3-hydroxyquinine in the plasma samples. The HPLC system consisted of an Agilent 1200 series HPLC system (Agilent Technologies, Santa Clara, California, USA) fitted with an isocratic pump (model G1341A). The variable wavelength detector [Agilent Technologies; standard version (model G1341B)] was set at 254 nm. Chromatographic separation was achieved with an Eclipse XDB-C18 reverse phase HPLC column, (5 μ m particle size and 150 $\times$ 4.6 mm, i.d.). The mobile phase consisting of (methanol: acetonitrile: 0.02M KH₂PO₄ buffer (15:15: 70) containing 0.64 ml of perchloric acid (70 % w/w, density 1.664 g/ml) to give a pH of 2.6 was run at a flow rate of 1.6 ml/min. Primaquine (3.0 μ g/ml) was used as the internal standard. Data acquisition was enabled by LC3D Chemstation software and windows 2000 for system Control. Sample extraction involved protein precipitation with perchloric acid, followed by basification with 5 M NaOH and subsequent extraction using diethylether and back extraction into 0.1M HCl. Calibration procedure has been previously reported. [32] Briefly, retention times of 3-hydroxyquinine, quinine and internal standard were 1.5, 2.7 and 6.7 min respectively. The Standard curve used in this study was linear over the concentrations range (0.25 – 4.0 μ g/ml) for both quinine and metabolite. The coefficient of determination was 0.999 and 0.9995 for quinine and 3 hydroxyquinine respectively. The limit of quantitation was 0.37 μ g/ml and 0.5 μ g/ml for quinine and for 3-hydroxyquinine respectively. Intraday and inter-day precision for both quinine and 3-hydroxyquinine ranged from 2.37 to 3.17 % and 1.49 to 3.51 %, respectively. Recovery was not less than 93.9 % for quinine and 73.4 % for 3-HQN, while accuracy for both quinine and its metabolite ranged between 93.1 % and 105.9 %.

Pharmacokinetic Analysis

$C_{\max}$ (peak plasma concentration), $t_{\max}$ (time to $C_{\max}$), were estimated by visual inspection of the plasma concentration-time profiles. Other pharmacokinetics parameters such as AUC_(0–48h) (area under the plasma concentration time curve), AUC_{0– ∞} (area under the plasma concentration time curve from zero to infinity), $T_{1/2}$ (terminal half-life), and Cl/F (apparent oral clearance), for quinine and 3-HQN were calculated by standard noncompartmental analysis using WinNonLin Standard Edition, version 1.5 Scientific Consultant Inc, Apex, NC, USA) using individual plasma concentration profile. AUC_(0–48h) were determined by the linear trapezoidal method to last sample time point. The area from the last datum point (C_t) to infinity was obtained as C_t/β . Linear regression analysis of the terminal phase of the log concentration-time profile was used to calculate the elimination rate constant (β). Elimination half life ($T_{1/2\beta}$) was computed from the elimination rate constant (β) as $0.693/\beta$. Cl/F was determined from dose/ AUC_{0– ∞} . Metabolic ratio was computed using the AUC_{0– ∞} met/AUC_{0– ∞} drug.

Statistical Analysis

Data were analysed using Minitab 17 by Lead Technologies, Inc. Pharmacokinetics parameters of quinine and 3-hydroxyquinine were summarized by descriptive statistics. The 90% confidence intervals (CIs) were constructed for the ratios of the geometric means of quinine with *G. kola* (T) and quinine alone (R) using a two one sided t-test for the primary

pharmacokinetic end points [$C_{\max}$ and $AUC_{0-\infty}$ of both quinine and 3-hydroxyquinine] and the metabolic ratio of 3-hydroxyquinine to quinine. The exponents of the ratios of the geometric means multiplied by 100 (point estimates) and that of the 90% CIs were computed. Bioequivalence was established if the 90% CIs were entirely within the 80–125% range and therefore no interaction was noted between periods. The Wilcoxon matched-pairs signed rank test at 95 % CI was used to evaluate differences between pairs of other pharmacokinetic data ($T_{\max}$, $T_{1/2}$, CL/F and Metabolic ratios) of quinine and its metabolite before and after subjects received *G. kola*

RESULTS

The twenty four volunteers were made up of eighteen male and six females. The age and weight [mean $\pm$ SD (range)] of group A was [24.00 $\pm$ 2.00 (21 – 28 years); 62.25 $\pm$ 7.77 (55 – 78 kg)] and group B was [23 .92 $\pm$ 3.06 (20–31years); 61.00 $\pm$ 7.80(46 – 77 kg)].

Figures 1 and 2 present the mean plasma concentration over time for quinine and 3-hydroxyquinine following oral administration of single oral doses of 600 mg of quinine sulphate before and after concurrent administration of scheduled dose of *G. kola*. Table 1 (Group A) summarizes the pharmacokinetic parameters (mean $\pm$ SD) for quinine and 3-hydroxyquinine following single oral administration of 600 mg dose of quinine sulphate tablet to each of 12 participants before and after each volunteer received *G. kola* (12.5 g) once daily for 7 days. Concurrent intake of *G. kola* with quinine resulted in reduction in peak plasma concentration ($C_{\max}$) and an increase in time to reach $C_{\max}$ ($t_{\max}$) of quinine. Specifically, $t_{\max}$ of quinine increased significantly by 48 %. ($p < 0.05$). Quinine and 3-hydroxyquinine $C_{\max}$ reduced by 19 % and 29 % respectively. The $C_{\max}$ of both quinine and its metabolite with and without *G. kola* administration were not bioequivalent as they fell outside the bioequivalence range of 80–125%. The exposure ($AUC_{0-\infty}$) to quinine and 3-hydroxyquinine, and also the metabolic ratio compared to baseline were bioequivalent (Table 2). Other parameters such as $T_{1/2}$ and CL/F for quinine were comparable to baseline ($p > 0.05$).

Table 1 (Group B) represents the pharmacokinetic parameters (mean $\pm$ SD) for quinine and 3-hydroxyquinine of twelve healthy volunteers following administration of 600 mg of quinine sulphate tablets alone and with *G. kola* (12.5 g) twice daily for 6 days and once on day 7. Quinine $t_{\max}$ increased by 27 % with concomitant intake of *G. kola*. The $C_{\max}$ of quinine and 3-hydroxyquinine decreased by 26 and 32 % respectively when compared to baseline. The $AUC_{0-\infty}$ of quinine was slightly reduced by about 9 %. Shown in Table 2 are the point estimate of T/R of $C_{\max}$ and $AUC_{0-\infty}$ for both quinine and 3-hydroxyquinine. The $C_{\max}$ of quinine and 3-hydroxyquinine, and also the $AUC_{0-\infty}$ of quinine fell outside the bioequivalence range of 80–125% when quinine was administered with *G. kola* on a twice-daily regimen.

Adverse effects of quinine

A questionnaire was designed and administered to the volunteers to record any observed side effects or adverse reaction during the study. The physician who assessed the volunteers for fitness to participate was also on site during drug administration and sample collection. No

adverse drug reaction was experienced that warranted discontinuation from the study. Blood pressure and pulse rate were monitored as drastic changes may be pointer to more serious adverse reaction to quinine. Following quinine administration, participants in the phase one of these studies tolerated the drug but presented with slight dizziness (18 participants), nausea (14 participants), headache (7 participants) and ringing sensation in the ear (4 participants). Interestingly, in the second phase, quinine was better tolerated. Precisely, only 3 participants complained of very light dizziness. There were no other complaints of adverse reactions reported by the volunteers

DISCUSSION

A major goal of an interaction study is to determine whether there is any increase or decrease in exposure to the substrate in the presence of the interacting drug, because this has a potential to influence therapy outcome. In this study, the $C_{\max}$ and $AUC_{0-\infty}$ consistently reduced (Figures 1 and 2) while $t_{\max}$ increased (Table 1) for both quinine and metabolite at both doses of *G. kola*. These observations suggest that co-administration of quinine and *G. kola* may have decreased and delayed the absorption of quinine. Furthermore, our findings (Table 2) clearly indicate there was a pharmacokinetic interaction between quinine and *G. kola* as evidenced from the 90 % confidence intervals of point estimates for $C_{\max}$ of quinine and 3-hydroxyquinine which fell outside the 80 – 125 % range in both groups. In considering the results of exposure ($AUC_{0-\infty}$) to quinine with concurrent *G. kola* administration, the ($AUC_{0-\infty}$) were bioequivalent at the 12.5 gm/day dose and not bioequivalent at the 12.5 gm twice daily dose of *G. kola*. Thus, an herb - drug interaction was noted with only the higher dose of *G. kola* as evidenced from the $C_{\max}$ and $AUC_{0-\infty}$ of quinine which were both reduced and not bioequivalent in the presence of 12.5mg twice daily dose of *G. kola* when compared with the baseline values. This suggests a dose dependent interaction may have occurred between *G. kola* and quinine. A plausible explanation for this occurrence may be that the presence of higher amount of *G. kola* (known to be rich in fiber) in the gut may have altered the systemic bioavailability of quinine. The metabolite exposure was considered important since it has been reported to contribute 5–12 % of the antimalarial action of quinine. [33] Our findings show that though the $AUC_{0-\infty}$ of metabolite in the presence of *G. kola* (12.5mg/day or 12.5mg twice daily) were reduced, they were however bioequivalent when compared to when quinine alone was administered.. From the foregoing, this change in the exposure to quinine at higher dose of *G. kola* coupled with a reduction in the peak plasma concentration of both quinine and 3-hydroxyquinine may suggest a potential to alter the outcome of oral quinine therapy.

The precise therapeutic window however remains uncertain as various factors have been reported to affect the pharmacokinetic and therapeutic response of quinine. [34, 35] In these present studies, the pharmacokinetic parameters of a single dose administration of quinine were in concordance with values reported in literature [36, 37]. Interestingly, we observed that during drug administration and blood sample collection, the incidences of adverse reactions to quinine was greatly reduced when *G. kola* was co-administered with quinine. Precisely, in the first phase, when quinine was administered alone, all the twenty four participants (100 %) complained of one or more mild adverse effects which were transient. However, in the second phase when quinine and *G. kola* were concurrently administered it

was much more tolerated. Out of the twenty four participants who participated in the study, only 3 participants (12.5 %) complained of slight dizziness while the other volunteers had no complaints of adverse reaction whatsoever to quinine. Indeed, the reduction in $C_{\max}$ and $AUC_{0-\infty}$ of quinine and its metabolite after concomitant intake of quinine with *G. kola* as observed in the current studies suggest a possible reduction in toxic effects or adverse effects of quinine. This observation is in agreement with previous report where higher plasma concentrations of quinine are associated with manifestations of toxic effects. [35]

There are several reports of other commonly consumed supplements with significant effects on drug bioavailability and disposition. For example, kola nut has been reported to cause a significant decrease in the plasma concentration of halofantrine and its metabolite when co-administered [28] and *Tamarindus indica* the major component of a local drink widely taken in the Northern part of Nigeria has been reported to significantly decrease the bioavailability of aspirin in healthy human subjects.[38]

Although, the exact mechanism responsible for the delayed and decreased absorption of quinine in the presence of *G. kola* in this current study is not known, it is possible that quinine may have interacted through complex formation with the trace metals or flavonoids usually found in *G. kola* [6, 11] as evidenced from a significant reduction in the $C_{\max}$ and $t_{\max}$ of quinine but no significant change in parameters which are indicative of interference with elimination. Since knowledge of the mechanism for interactions makes it possible to predict and prevent pharmacokinetic drug interactions [39], further studies are necessary to investigate the different mechanisms of interactions leading to a decrease in the plasma concentrations of quinine when co-administered with *G. kola*.

To determine whether the extracts of *G. kola* seeds influence Phase I and Phase II drug metabolizing enzymes [12–14] we also evaluated the possible modulation of enzyme activity by *G. kola* by using the metabolic ratio of quinine in plasma [26] as a measure of the assessment of metabolism of quinine to 3-hydroxyquinine by CYP3A, in both groups. The metabolic ratio of 3-hydroxyquinine to quinine did not change significantly in the presence of *G. kola* suggesting that the activity of CYP3A in metabolising 3-hydroxyquinine to quinine was not significantly modulated in the presence of *G. kola*. Moreover, parameters such as $T_{1/2}$ and CL/F of quinine that relates to elimination in both study groups were also not altered significantly in the presence of *G. kola*. We argue that the observed reduction in the plasma concentrations of quinine in healthy volunteers in the presence of *G. kola* may not be due to a metabolic interaction or interference but rather a potential reduction in absorption. It is possible that CYP3A activity on quinine metabolism in humans is not significantly affected by co-administration of *G. kola*.

Co-administration of oral quinine and *G. kola* seeds resulted in a reduction in the peak plasma concentrations and exposure of quinine and its major metabolite, 3 hydroxyquinine. The absorption of quinine was delayed as evidenced from an increase in the $T_{\max}$ of quinine. A pharmacokinetic herb-drug interaction was seen with the $C_{\max}$ of quinine and its metabolite at both doses of *G. kola* seed and with quinine exposure ($AUC_{0-\infty}$) at only the higher dose of *G. kola* seed. Therefore, caution may need to be exercised with the ingestion of *G. kola* when on oral quinine therapy.

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Figure 1. Mean plasma concentration versus time profiles for quinine and 3-hydroxyquinine following single oral administration of 600mg dose of quinine sulphate tablet to 12 volunteers before and after each volunteer received *G. kola* (12.5 g) once daily for 7 days (Group A)

Figure 2. Mean plasma concentration versus time profiles for quinine and 3-hydroxyquinine following single oral administration of 600mg dose of quinine sulphate tablet to 12 volunteers before and after each volunteer received *G. kola* (12.5 g) twice daily for 6 days and once on day 7 (Group B)

Table 1

Summary of mean pharmacokinetic parameters of quinine and 3-hydroxyquinine following oral administration of 600 mg of quinine sulphate tablets alone and with intake of 12.5 g of *G. kola* once daily for 7 days (Group A) or with 12.5 g of *G. kola* twice daily for 6 days and once on day 7 (Group B)

	GROUP A		GROUP B	
	Quinine alone	Quinine and <i>G. kola</i> (12.5 g once daily)	Quinine alone	Quinine and <i>G. kola</i> (12.5 g twice daily)
Quinine				
T _{max} (h)	2.9 (1 – 4)	3.8 (1 – 6)	2.4 (1– 4)	3.1 (2 – 6)
C _{max} (µg/ml)	3.9 ± 0.6	3.2 ± 0.9	4.1 ± 0.9	3.0 ± 0.6
AUC _{0–∞} (h µg/ml)	58.6 ± 9.0	53.0 ± 7.6	59.6 ± 19.2	54.2 ± 16.5
T _{1/2} (h)	11.9 ± 3.4	13.2 ± 2.5	12.7 ± 1.9	13.3 ± 3.0
CL/F (L/h)	10.5 ± 1.9	11.5 ± 1.5	11.0 ± 3.4	12.0 ± 3.3
3-Hydroxyquinine				
T _{max} (h)	3.3 (1 – 8)	3.1(1 – 8)	2.3(1– 3)	2.7 (1– 4)
C _{max} (µg/ml)	0.9 ± 0.3	0.6 ± 0.2	0.7 ± 0.2	0.5 ± 0.1
AUC _{0–∞} (h µg/ml)	21.5 ± 2.7	18.7 ± 2.6	16.5 ± 2.3	15.1 ± 2.2
AUC _{0–∞} met/AUC _{0–∞} drug	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1

Values are mean ± SD (n = 12 respectively); range for T_{max}, C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; AUC_{0–∞}, area under the plasma concentration time curve from zero to infinity; T_{1/2}, terminal elimination half-life; CL/F, oral plasma clearance

Table 2

Statistical analysis of primary pharmacokinetic end point following administration of 600 mg of quinine sulphate tablets alone and with *G. kola* of 12.5 g one daily for 7 days (Group A) or twice daily for 6 days and once on day seven (Group B) to 12 healthy volunteers respectively.

T/R point estimate multiplied by 100 (90% CI)	
GROUP A	
Quinine	
$C_{\max}$ (µg/ml)	78.7 (66.4, 93.5) *
$AUC_{0-\infty}$ (h µg/ml)	90.7 (81.5, 100.5)
3-Hydroxyquinine	
$C_{\max}$ (µg/ml)	70.9 (56.8, 88.5) *
$AUC_{0-\infty}$ (h µg/ml)	87.0 (80.7, 94.0)
$AUC_{0-\infty \text{ met}}/AUC_{0-\infty \text{ drug}}$	96.0 (84.2, 109.5)
GROUP B	
Quinine	
$C_{\max}$ (µg/ml)	74.4 (64.2, 86.4) *
$AUC_{0-\infty}$ (h µg/ml)	91.6 (74.0, 113.3) *
3-Hydroxyquinine	
$C_{\max}$ (µg/ml)	68.5 (59.8, 78.4) *
$AUC_{0-\infty}$ (h µg/ml)	91.6 (86.4, 97)
$AUC_{0-\infty \text{ met}}/AUC_{0-\infty \text{ drug}}$	100.0 (91.4, 109.4)

Values are mean $\pm$ SD (n = 12); $C_{\max}$, maximum plasma concentration; $AUC_{0-\infty}$, area under the plasma concentration time curve from zero to infinity, $AUC_{0-\infty}$ area under the plasma concentration time curve from zero infinity.

* (bio-inequivalent)