

Influence of Amlodipine on the Disposition of Quinine in Healthy Volunteers

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Concurrent administration of 2 or more drugs in patients with co-existing diseases is a common practice. However, this practice increases the complexity of pharmacotherapy and may result in significant drug–drug interactions.¹ Patients with hypertension generally require concomitant antimalarial therapy when they present with concurrent malaria infection. With the widespread incidence of malaria and hypertension in the low- and middle-income countries, concurrent administration of therapies for these 2 conditions may arise. Despite the advent of artemisinin-based combination therapies, quinine remains a viable therapeutic option in malaria chemotherapy mainly because of rising resistance to artemisinin-based combination therapies, in some regions.² On the other hand, amlodipine, a longacting third-generation dihydropyridine calcium channel blocker, is commonly prescribed for the management of hypertension.^{3,4} Because quinine and amlodipine are substrates for both cytochrome P450 (CYP) drug-metabolizing enzymes and the transporter, P-glycoprotein, and amlodipine also inhibits both drug metabolizing and transporter activities,^{5–10} concurrent administration of the 2 drugs may result in potential drug–drug interactions. Previous studies found that coadministration of quinine with substrates and inhibitors of CYP3A4 resulted in a significant increase in the systemic exposure of quinine.^{11,12} This study investigated the effect of the coadministration of amlodipine on quinine pharmacokinetics.

A two-phase, randomized, crossover pharmacokinetic study was implemented. The study was approved by the Health Research Ethics Committee of the Institute of Public Health of the Obafemi Awolowo University, Ile-Ife, Nigeria. The study population included healthy nonsmoking individuals, aged 18–36 years and weighing 45–71 kg. Subjects with previous or current evidence of gastrointestinal, psychiatric, cardiovascular, or neurological disorders were excluded from the study. All subjects provided informed consent before enrollment into the study. Subjects were randomly divided into 2 groups, and a single dose of 600 mg quinine was administered alone or with 5 mg of amlodipine in a crossover fashion. Blood samples were collected predose and at intervals over 48 hours and analyzed for quinine and its metabolite, 3-hydroxyquinine (3-HQN) using a validated high-performance liquid chromatographic method. Briefly, 200 mL of plasma

was transferred into a 10 mL extraction tube and deproteinated with 200 mL of perchloric acid by whirl-mixing for

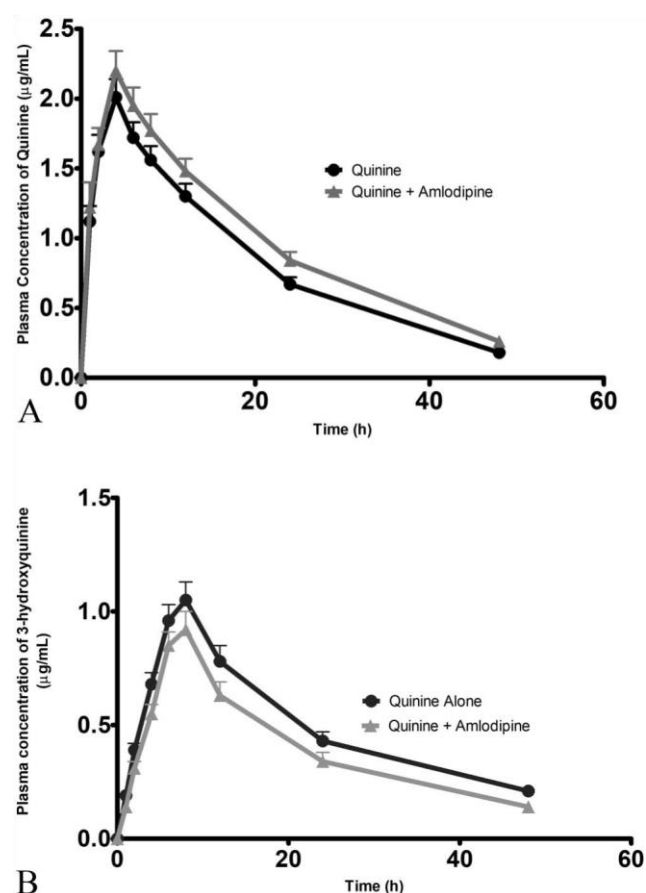


FIGURE 1. Mean concentration–time profile of quinine (A) and 3-hydroxyquinine (B) after single oral dose of 600 mg quinine with or without single oral dose of 5 mg amlodipine.

5 seconds in the presence of 50 mL of a 100 mg/mL phenacetin solution (internal standard). This was followed by the addition of 1 mL of 5M NaOH and extraction of the drug and its metabolite in 4 mL of diethyl ether by whirl-mixing for 1 minute. The tube was centrifuged at 33000g for 10 minutes, and the ethereal layer was transferred into a new 10 mL extraction tube, and 200 mL of 0.1M HCl was added. The resulting solution was whirl-mixed for 1 minute, centrifuged for 5 minutes at 33000g, and the aqueous layer was injected into the high-performance liquid chromatographic column. Pharmacokinetic and

statistical analyses were performed using Kinetica software version 4.1 and Wilcoxon matched-pair signedranked test, respectively. Vital pharmacokinetic parameters derived from the 2 groups were compared by calculating the geometric mean ratio at 90% confidence intervals. Two of the 15 subjects enrolled in the study withdrew after quinine administration because of inability to cope with the sampling protocol. The investigated drugs were generally well-tolerated, and none of the subjects experienced serious drugrelated side effects. The method

mg/mL), ranged from 91.73% to 95.60% for quinine and between 92.03% and 96.88% for 3-hydroxyquinine. The method of analysis was precise, with precision ranging between 2.2% and 4.9% for quinine, 3.6% and 5.6% for 3-hydroxyquinine, for both interday and intraday precision analysis.

The concentration–time profile of quinine and 3-hydroxyquinine, with or without amlodipine, is shown in Figure 1. Amlodipine significantly increased the AUC_{0–N}

Table 1. Pharmacokinetic parameters of quinine and 3-hydroxyquinine following administration of a single oral dose of 600 mg quinine alone and concurrently with 5 mg single oral dose of amlodipine.

Parameters	Quinine alone	Quinine + amlodipine	GMR (90% CI)	P
Quinine				
AUC _{0–48h} (mg\$h/mL)	39.65 (35.89–47.70)	46.87 (41.85–54.70)	1.18 (1.11–1.26)	0.0017*
C _{max} (mg/mL)	2.18 (1.92–2.59)	2.40 (2.03–2.75)	1.11 (1.01–1.21)	0.0017*
C _{min} (mg/mL)	0.17 (0.15–0.21)	0.27 (0.19–0.37)	1.48 (1.20–1.84)	0.002*
AUC _{0–N} (mg\$h/mL)	41.97 (37.86–50.85)	52.24 (46.47–60.30)	1.22 (1.11–1.38)	0.0002*
Cl/F (L/h)	14.30 (11.85–15.85)	11.49 (9.95–12.96)	0.82 (0.72–2.90)	0.0002*
t _{1/2} (h)	12.79 (12.52–12.93)	14.81 (14.61–15.38)	1.15 (1.02–1.32)	0.0002*
t _{max} (h)	4.00 (3.00–4.00)	4.00 (2.00–4.00)	0.98 (0.50–1.00)	0.337
MR	0.64 (0.46–0.77)	0.44 (0.31–0.52)	0.67 (0.52–0.80)	0.0017*
3-Hydroxyquinine				
AUC _{0–48h} (mg\$h/mL)	24.57 (19.20–28.63)	20.22 (15.00–22.74)	0.79 (0.64–0.88)	0.0002*
C _{max} (mg/mL)	1.20 (0.96–1.28)	1.03 (0.80–1.16)	0.87 (0.75–0.96)	0.0002*
C _{min} (mg/mL)	0.17 (0.12–0.20)	0.11 (0.10–0.14)	0.70 (0.50–0.92)	0.0016*
AUC _{0–N} (mg\$h/mL)	25.23 (20.30–27.07)	20.33 (16.03–22.49)	0.81 (0.56–0.93)	0.0002*
Cl/F (L/h)	23.78 (22.17–29.84)	29.52 (26.73–38.43)	1.27 (1.07–1.77)	0.0002*
MRT (h)	20.05 (18.51–27.70)	19.26 (17.21–26.97)	0.94 (0.92–0.95)	0.0002*
T _{max} (h)	8.00 (6.00–8.00)	8.00 (6.00–8.00)	1.06 (1.00–1.50)	0.1959

Values are expressed as median (IQR, interquartile range).

AUC_{0–N}, area under the curve from time 0 to infinity; AUC_{0–48h}, area under the curve from time 0–48 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; Cl/F, apparent total clearance; T_{max}, time to C_{max}; t_{1/2}, terminal elimination half-life; CI, confidence interval; GMR, Geometric Mean Ratio; MR, metabolic ratio; MRT, Mean Residence Time.

*Statistically significant.

of analysis was sufficiently robust for the determination of quinine and 3-hydroxyquinine in plasma and plasma matrices did not interfere with the outcome of the analysis. The retention times for 3-hydroxyquinine, quinine and phenacetin were 2.5, 3.4, and 4.5 minutes, respectively, whereas the recoveries for quinine and 3-hydroxyquinine were 94.56% and 93.84%, respectively. The accuracy of the analytical procedure, measured at 3 different range of concentrations (0.1, 2, and 5

(41.97–52.24 mg\$h/mL) and C_{max} (2.18–2.40 mg/mL) of quinine after concurrent administration with amlodipine (Table 1). However, quinine clearance decreased by 19.65% while the time to reach C_{max} (ie, T_{max}) remained unchanged in the presence of amlodipine. Though statistically significant, these changes appear not to be clinically significant as the geometric mean ratios of key pharmacokinetic parameters of quinine (AUC_{0–48h}, AUC_{0–N} and C_{max}) fell within FDA recommended range of 80%–125%.¹³

[0.64 (0.46–0.77) to 0.44 (0.31–0.52)]. The major route of quinine metabolism to 3-hydroxyquinine is via the CYP3A4 subfamily. The inhibition of this enzymatic pathway may increase the C_{max} , AUC_{0-48h} and AUC_{0-N} of quinine, as observed in this study. Inhibition of CYP3A4 activity by amlodipine has been previously reported. For instance, concurrent amlodipine administration increased the AUC and C_{max} of simvastatin by 42.7% and 27.9%, respectively.¹⁴ This interaction was reported in a later study to be attenuated by a nonconcurrent dosing regimen.¹⁵ The quinine metabolic ratio and plasma level of 3HQ decreased significantly in the coadministration group, an observation that further suggests the inhibition of quinine metabolism via the CYP3A4 pathway. The observed changes in the plasma exposure of quinine with concurrent amlodipine administration may also be attributed to a concentration-dependent inhibition of the P-gp-mediated transmembrane efflux of quinine by amlodipine. However, this mechanism is unlikely to account for these changes as the apparent clearance of quinine decreased after concurrent administration with amlodipine. The use of healthy volunteers in this study may be considered a limitation because plasma concentrations of quinine are known to be higher in malaria-infected individuals, because of the raised level of alpha-1-acid glycoprotein.¹⁶ Further investigations in patients with malaria infection, as well as malaria and hypertension comorbidity, may be required to clarify the magnitude and clinical significance of this interaction.

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The authors have no conflicts of interest to declare.

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