JPP
Journal of
Pharmacy and Pharmacology

JPP 2009, 61: 439–443

Received October 6, 2008
Accepted December 22, 2008
DOI 10.1211/jpp/61.04.0004
ISSN 0022-3573

Research Paper

Effects of concurrent administration of nevirapine on the disposition of quinine in healthy volunteers

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Abstract

Objectives Nevirapine and quinine are likely to be administered concurrently in the treatment of patients with HIV and malaria. Both drugs are metabolised to a significant extent by cytochrome P450 (CYP)3A4 and nevirapine is also an inducer of this enzyme. This study therefore evaluated the effect of nevirapine on the pharmacokinetics of quinine.
Methods Quinine (600 mg single dose) was administered either alone or with the 17th dose of nevirapine (200 mg every 12 h for 12 days) to 14 healthy volunteers in a crossover fashion. Blood samples collected at predetermined time intervals were analysed for quinine and its major metabolite, 3-hydroxquinine, using a validated HPLC method.
Key findings Administration of quinine plus nevirapine resulted in significant decreases ($P < 0.01$) in the total area under the concentration–time curve (AUC_T), maximum plasma concentration (C_{max}) and terminal elimination half-life ($T_{½\beta}$) of quinine compared with values with quinine dosing alone (AUC: 53.29 ± 4.01 vs 35.48 ± 2.01 h mg/l; C_{max}: 2.83 ± 0.16 vs 1.81 ± 0.06 mg/l; $T_{½\beta}$: 11.35 ± 0.72 vs 8.54 ± 0.76 h), while the oral plasma clearance markedly increased (11.32 ± 0.84 vs 16.97 ± 0.98 l/h). In the presence of nevirapine there was a pronounced increase in the ratio of AUC(metabolite)/AUC (unchanged drug) and highly significant increases in C_{max} and AUC of the metabolite ($P < 0.01$).
Conclusions Nevirapine significantly alters the pharmacokinetics of quinine. An increase in the dose of quinine may be necessary when the drug is co-administered with nevirapine.
Keywords 3-hydroxyquinine; nevirapine; pharmacokinetic interaction; quinine

Introduction

The prevalence of malaria and HIV as well as the extent of their geographical overlap vary widely within different regions. In countries with high prevalence of both infections, co-infection is common; hence, the possibility of a patient taking an antimalarial and an antiretroviral drug concurrently is very high.[1] The occurrence of resistance to chloroquine and sulphadoxine–pyrimethamine by the malaria parasite in Southern Asia, Africa and South America has stimulated renewed interest in quinine as an alternative drug for treating multi-drug resistant *Plasmodium falciparum* malaria.[2] Quinine is available in oral and injectable formulations and it has tolerable side effects if used correctly and at the normal therapeutic doses.[2] It is the drug of choice for the management of severe malaria in most areas of the world, and is frequently used in conditions where intravenous infusions cannot be rapidly established or reliably monitored.[3] The drug is also important during pregnancy for the treatment of severe and multidrug-resistant *P. falciparum* malaria.[4] However, in recent years there have been concerns that the efficacy of quinine is declining in some parts of South-east Asia, and quinine resistance has been documented in Africa.[5,6] However, a series of trials to find drugs that are suitable alternatives to quinine have demonstrated that quinine is as effective as the artemisinin derivatives, artesunate and artemether.[7,8] Quinine is mainly metabolised to its major metabolite, 3-hydroxyuinine (3-HQN), by cytochrome P450 (CYP)3A4.[9,10]

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which interrupts the reverse transcription of viral RNA to DNA, a crucial step for HIV replication.[11] Each of the NNRTIs is metabolised to some degree by the cytochrome P450 system of enzymes, making them prone to clinically significant drug interactions.[12] In addition, they elicit

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variable effects on other drugs, acting as either inducers or inhibitors of the metabolising enzymes. Data from in-vitro and in-vivo studies indicate that nevirapine is principally metabolised by CYP3A4, and to a minor extent by CYP2B6. It also induces both enzymes but has little potential to be involved in inhibitory drug interactions.[13–15]

Since both quinine and nevirapine are substrates for CYP 3A4, there is a potential for a pharmacokinetic interaction between these two agents via this metabolic pathway. However, the magnitude and clinical significance of such an interaction can only be evaluated through studies. HIV-positive patients receiving treatment with nevirapine may require concomitant treatment with quinine for malaria infection. The pharmacokinetic interaction between nevirapine and an antimalarial, lumefantrine–artemether (Coartem), has been investigated. Both lumefantrine and artemether are substrates for CYP3A4, and nevirapine was found to significantly induce the metabolism of these drugs.[16]

The aim of the present study was to determine the effect of concurrent administration of multiple doses of nevirapine on the disposition of quinine in healthy volunteers.

Methods

Subjects

Fourteen healthy volunteers (eight men and six women) aged 19–27 years and weighing 49–67 kg were enrolled into the study after giving written informed consent. Before entry into the study, volunteers were certified healthy by Dr AR Owolabi, who is a physician, on the basis of medical history, clinical examination and biochemical and haematological screening. None of the subjects had received any other drugs for at least 1 month before the study and none were smokers. Subjects were excluded from participating if they were pregnant, breastfeeding, had a history of hypersensitivity reactions to NNRTIs, quinine or similar agents, or evidence of a history, or physical evidence on examination, of gastrointestinal, psychiatric, cardiovascular or neurological disorders. Approval for the study protocol was obtained from the Obafemi Awolowo University Teaching Hospital Research Ethics Board and Safety Committee.

Study design and drug administration

The study was an open-label, randomised, two-period crossover pharmacokinetic study. After an overnight fast, each volunteer received a single oral 600 mg dose of quinine sulfate (quinine sulfate tablets, Eli Lilly and Co., Indianapolis, IN, US), either alone or with the 17th dose of nevirapine (on day 9). Volunteers took nevirapine (Strides Areolab Ltd, Bangalore, India), 200 mg, as a single oral dose every 12 hours for 12 days. A washout period of 3 weeks was allowed between the two arms of the study. No other drugs or alcohol was permitted during the study.

Sample collection

Before drug administration, venous blood samples (5 ml) were collected from all subjects for determination of serum chemistry and haematological screening. Thereafter, blood samples (5 ml) were withdrawn by venipuncture into heparinised tubes from the forearm of each subject before quinine administration and at 1, 2, 4, 6, 8, 12, 24, 36 and 48 hours afterwards. The samples were centrifuged immediately (1500*g* for 10 min) to separate the plasma. The plasma aliquots were stored at −20°C until analysis.

Drug analysis

Plasma samples were analysed for quinine and 3-HQN using the HPLC method reported by Babalola *et al.*,[17] with the following modifications. Pyrimethamine was used as the internal standard (20 μl of a 500 μg/ml solution in 1 ml plasma) rather than primaquine, and we used a 5-μm particle size C18 column (200 × 4.6 mm I.D.; Agilent Technologies, Palo Alto, CA, US) to achieve peak resolution and to ensure no interference from nevirapine. Sample extraction involved alkanisation of the plasma with NaOH, followed by extraction with diethylether and back-extraction into 0.1 M HCl. The calibration procedures were as reported.[17] The HPLC equipment was an AKTA system (Amersham Pharmacia Biotech, Uppsala, Sweden) consisting of binary pumps (P-900) fitted with a gradient mixer and a variable wavelength (200–800 nm) model UV-900 detector. Samples were injected via a model INV-907 valve fitted with a 50 μl loop. The detector output was linked via a brain box interphase (AKTA) to a computer with a chromatography data system package. The mobile phase consisted of methanol : acetonitrile : 0.02 M potassium dihydrogen phosphate (15 : 10 : 75 v/v) containing 75 mmol/l perchloric acid (pH 2.8), delivered at a flow rate of 1.0 ml/min. The column effluent was monitored at 254 nm. The retention times of 3-HQN, quinine and the internal standard were 4, 7 and 12 min, respectively. The coefficients of variation for both the intra-day and inter-day analysis ranged from 1.10 to 3.57% for quinine, and from 2.75 to 3.26% for 3-HQN. The absolute recovery was over 92% for the two compounds at concentrations at the lower and upper limits of their calibration curves (0.5 and 4 μg/ml).

Data and statistical analysis

The peak plasma concentrations (C_{max}) and the time to reach peak concentration (T_{max}) were noted directly from the concentration–time profiles. Other pharmacokinetic parameters such as terminal elimination half-life ($T_{½\beta}$) and oral clearance (CL/F) were calculated from individual plasma concentration–time profiles, using standard non-compartmental methods.[18] For example, the total area under the plasma concentration–time curve (AUC_T) was determined using the linear trapezoidal rule to the last datum and extrapolation to infinity. The area from the last datum points (C_t) to infinity was obtained as C_t/β. The elimination rate constant, β, was calculated by linear regression analysis of the terminal phase of the log concentration–time profile. $T_{½\beta}$ was calculated from $0.693/\beta$ and Cl/F was determined from dose/AUC_T. Pharmacokinetic calculations were done using the pharmacokinetic program WinNonlin (standard edition, Version 1.5, Scientific Consultant Inc. Apex, NC, US). In the model option for the non-compartmental analysis, the linear trapezoidal rule was used for calculation of the AUC.

The Wilcoxon matched pairs signed-ranked test was used to evaluate the difference between pairs of data; a P value below 0.05 was considered significant.

Results

Figure 1 shows the mean plasma concentration–time profiles of quinine and 3-HQN following oral administration of single doses of 600 mg of quinine sulfate alone, and with nevirapine, to the 14 volunteers. The derived pharmacokinetic parameters for quinine following administration of the drug with and without nevirapine are presented in Table 1.

Concurrent administration of nevirapine resulted in a significant reduction in the AUC_T, C_{max} and $T_{½}$ of quinine compared with values obtained following administration of the antimalarial alone ($P < 0.01$, Table 1). These show a decrease in AUC_T by 33% (95% confidence intervals (CI): 28–38%), while C_{max} decreased by 36% (95% CI: 33–40%) and $T_{½\beta}$ decreased by 25% (95% CI: 19–31%). On the other hand, the oral plasma clearance of quinine was markedly enhanced in the presence of nevirapine – by about 50% (95% CI: 43–57%), although values for T_{max} were comparable in the presence and absence of nevirapine.

Pharmacokinetic parameters of 3-HQN following administration of quinine with and without nevirapine are also shown in Table 1. The C_{max} and $AUC_{0–48h}$ of the metabolite were significantly elevated in the presence of nevirapine ($P < 0.01$). The C_{max} increased by 25% (95% CI: 19–31%) while $AUC_{0–48h}$ increased by 30% (95% CI: 24–37%). Concurrent nevirapine administration also resulted in a pronounced enhancement of the ratio of the AUC of metabolite to that of unchanged drug (metabolic ratio) by about 90% (95% CI: 80–97%). There was no significant

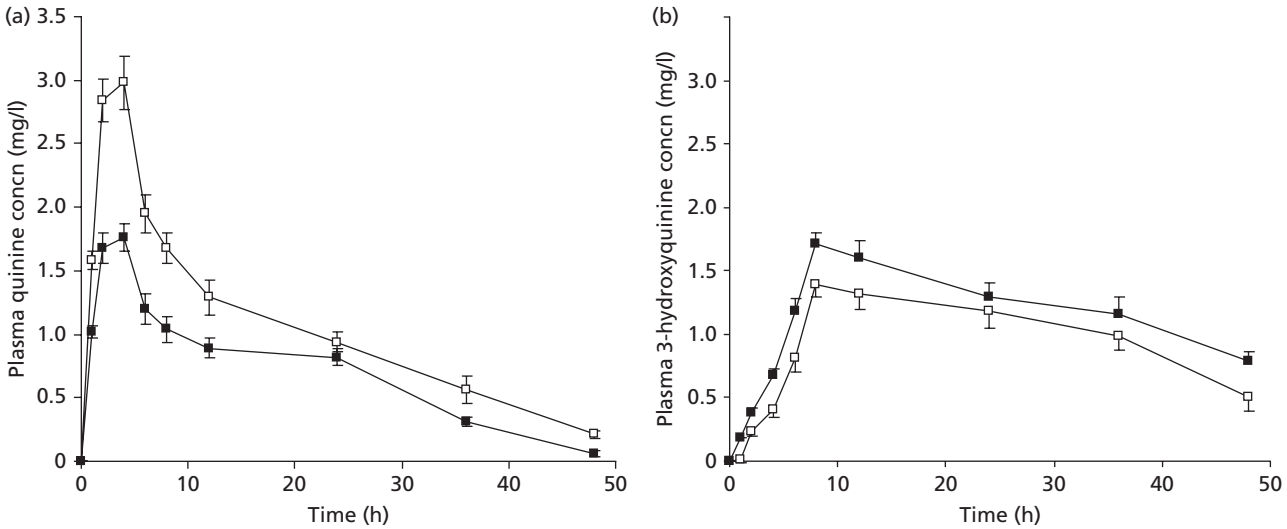

Figure 1 Plasma concentration vs time profiles of (a) quinine and (b) 3-hydroxyquinine. A single oral dose of quinine sulfate (600 mg) was administered either (□) alone or (■) with the 17th dose of multiple oral doses of nevirapine (200 mg every 12 h for 12 days), to 14 healthy volunteers. Values are means ± SD.

Table 1 Mean pharmacokinetic parameters of quinine and its major metabolite, 3-hydroxyquinine, following administration of a single oral dose of quinine sulphate (600 mg) either alone or after multiple doses of nevirapine (200 mg every 12 h for 12 days)

	Quinine alone	Quinine with nevirapine	Mean difference (95% CI)
Quinine			
T_{max} (h)	3.43 (2–4)	3.57 (2–4)	0.14 (–0.17, 0.45)
C_{max} (μg/ml)	2.83 ± 0.16	1.81 ± 0.06	–1.03 (–1.13, –0.94)*
$T_{½\beta}$ (h)	11.35 ± 0.72	8.54 ± 0.76	–2.81 (–3.46, –2.16)*
AUC_T (h μg/ml)	53.29 ± 4.01	35.48 ± 2.01	–17.82 (–20.43, –15.2)*
Cl/F (l/h)	11.32 ± 0.84	16.97 ± 0.98	5.65 (4.91, 6.4)*
3-hydroxyquinine			
T_{max} (h)	8.86 (8–12)	9.14 (8–12)	0.29 (–1.40, 1.97)
C_{max} (μg/ml)	1.39 ± 0.12	1.74 ± 0.10	0.34 (0.26, 0.43)*
$AUC_{0–48h}$ (h μg/ml)	43.22 ± 3.68	56.46 ± 4.41	13.04 (10.30, 15.77)*
Metabolic ratio	0.88 ± 0.10	1.65 ± 1.01	0.78 (0.70, 0.85)*

Values are mean ± SD ($n = 14$); range for T_{max}. *$P < 0.01$. AUC_T, total area under the concentration–time curve; $AUC_{0–48h}$, area under the concentration–time curve from 0 to 48 h; CL/F, oral plasma clearance; C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; $T_{½\beta}$, terminal elimination half-life.

change in the T_{max} of 3-HQN. The apparent half-life of the metabolite derived from the terminal phase of its concentration–time profile following administration of quinine alone was 20.08 ± 6.3 h. This shows that $k > k_m$, where k and k_m are the elimination rate constants of the parent drug and metabolite, respectively. This indicates that metabolite elimination is elimination-rate limited.

Discussion

This study was designed to evaluate the plausible interaction between quinine and nevirapine. There is a constant stream of new information about drug interactions in patients with HIV infection and, with so many new drugs in clinical development, this is an area that will continue to be an important aspect of treatment. Nevirapine has been shown to have the potential to interact with a range of other drugs, and healthcare providers need to be aware of the basis of these interactions and the potential impact on therapy.

The results from this study indicate that quinine is rapidly absorbed after oral administration in all subjects, with an average T_{max} of 2–4 h. The pharmacokinetic parameters obtained for the drug when administered alone, such as T_{max}, elimination $T_{½}$, Cl/F and AUC_T, were in general agreement with values reported in the literature.[4,19–22] In healthy subjects, quinine undergoes extensive biotransformation and less than 20% of the drug is excreted unchanged in urine. Its metabolism is mediated mainly by CYP3A4 and to a minor extent by CYP2C9.[9,10,23] In humans, nevirapine is also extensively metabolised via cytochrome P450 to several hydroxylated metabolites. Studies with human liver microsomes suggest that the metabolic pathway is primarily mediated by CYP3A4 and to a lesser degree by CYP2B6.[13,24] Nevirapine has been reported to be an inducer of CYP3A4.[14,15] Therefore, the observed decrease in plasma quinine exposure found in this study, seen as significant decreases in C_{max}, $T_{½}$ and AUC_T of the drug following concurrent administration of nevirapine, is most probably attributable to induction of CYP3A4 by nevirapine, the enzyme that catalyses formation of 3-HQN. This assertion is supported by the observed corresponding increase in the C_{max} and AUC of the metabolite. Several drug interaction studies with nevirapine have shown that plasma levels of other CYP3A4 substrates are significantly reduced in the presence of the NNRTI.[15] For example, significant reductions in the AUC of saquinavir and indinavir by co-administration of nevirapine have been reported.[25,26] Also, the plasma levels of efavirenz were significantly reduced in the presence of nevirapine, with the AUC decreasing by 22% and the minimum plasma concentration by 36%.[27] Of particular significance is the effect of nevirapine on plasma methadone concentrations, which were reduced by about 50% in patients on maintenance therapy after 7–10 days of nevirapine.[28] Nevirapine has also been reported to markedly induce CYP3A4 in the gut wall.[29] The comparable decreases in the AUC and C_{max} of quinine (33 and 36%, respectively) were greater than the decrease (24%) obtained for the $T_{½}$ of the drug in the presence of nevirapine. This suggests that pre-systemic induction of CYP3A4 also contributes to the decreased plasma drug levels. This can also be considered from the aspect of metabolite kinetics: the mean half-life obtained from the terminal phase of the plasma concentration–time profiles of the metabolite was longer than the value for quinine. The shorter elimination half-life of the parent compound compared with that of its metabolite indicates that elimination of the metabolite is elimination-rate limited rather than formation-rate limited. Hence, elevated plasma levels of the metabolite could be attributed to induction of systemic CYP3A4 activity. Also, the significant reduction in the elimination half-life of quinine in the presence of nevirapine observed in this study, which further supports the induction effect of nevirapine as a systemic action, has been reported for other drugs such as ethinylestradiol and itraconazole when co-administered with nevirapine.[24,30]

The marked increase in the metabolic ratio of quinine further strengthens the point that a metabolic interaction occurs between quinine and nevirapine, and that nevirapine induces the metabolism of quinine. This raised level of 3-HQN due to nevirapine co-administration may reduce the efficacy of quinine as an antimalarial while simultaneously increasing toxicity, since 3-HQN is reported to have a higher toxicity and a lower antimalarial activity than its parent compound.[31] Since quinine has a narrow therapeutic window,[31] the decrease in C_{max} of up to 40% and 38% decrease in AUC of the drug in the presence of nevirapine are likely to be of clinical significance. Thus, adjustment of the quinine dose may be necessary when the drug is co-administered with nevirapine. The potential increase in toxicity that may be associated with elevated plasma levels of 3-HQN should also be noted.

Conclusions

This study demonstrated that concurrent administration of nevirapine, a known inducer of CYP3A4, with quinine, a substrate of the isoenzyme, results in a significant reduction in the plasma levels of the antimalarial. Plasma levels of 3-HQN, the major metabolite of quinine, are elevated in the presence of nevirapine. Adjustment of the quinine dose may be necessary when the drug is co-administered with nevirapine, but this should be balanced against the potential increase in toxicity that may be associated with elevated plasma levels of the metabolite.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This work was supported by Obafemi Awolowo University, Ile-Ife, Nigeria, Research grant no. 11813 AEC.

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