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Ototoxic reactions of quinine in healthy persons and patients with *Plasmodium falciparum* infection

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Abstract

Audiometric changes following quinine administration were studied in healthy Caucasian subjects and patients suffering from falciparum malaria disease. Quinine-dihydrochloride was administered intravenously as a single dose of 300 mg to 12 healthy subjects and as multiple doses of 600 mg in 4 h every 8 h in 10 *Plasmodium falciparum* malaria patients. The hearing function was monitored by conventional and high frequency audiometry. In nine healthy subjects hearing loss was documented at 2–4 h after infusion of Quinine-dihydrochloride at a mean maximal plasma quinine concentration of only 2 mg/l. In one healthy subject a persistent loss occurred of 20 dB at 14 kHz in one ear. In all malaria patients severe hearing losses and adverse effects related to ototoxicity were documented, but all the audiograms had returned to normal after 1 week and side effects disappeared. This study has shown that ototoxicity induced by quinine is almost completely reversible in healthy volunteers and in malaria patients. © 1997 Elsevier Science Ireland Ltd.

Keywords: Quinine; Ototoxicity; Malaria

1. Introduction

Quinine has been used in the treatment of malaria since the early 1600s. The first side effect of the treatment of quinine for malaria has already been reported by Richard Morton in 1692. He described the treatment with quinine for malaria as rather safe: "I have never known anyone suffer a misfortune as a result of using Cinchona bark (Quinine) other than a distressing type of hearing loss" [1].

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Quinine is an effective drug in suppressing the acute attack of malaria. Intravenous quinine is the initial treatment of severe *Plasmodium falciparum* malaria since the occurrence of chloroquine resistant strains of the parasite has become widespread.

Small doses of quinine can cause tinnitus in susceptible persons [2]. Because of the lack of clinical significance the interest in the ototoxicity of quinine has been subdued.

This paper reports on the ototoxic reactions of quinine in healthy persons and patients with *Plasmodium falciparum* infections with the focus on the reversibility of this drug.

2. Material and methods

To 12 healthy Dutch volunteer subjects (8 males, 4 females; age 19–32 years; bodyweight 51–80 kg) a single dose of 300 mg quinine-dihydrochloride (quinine-di-HCl) in 500 ml normal saline was administered intravenously (iv) in 4 h. To 9 Caucasian patients (5 men, 4 women; age 20–49 years, bodyweight 53–88 kg) with single species *P. falciparum* malaria 600 mg quinine-di-HCl in 500 ml normal saline was given in 4 h, every 8 h, for 3 days. All these patients acquired malaria in Africa. The diagnosis was confirmed by thick and thin bloodsmears (parasite counts 120–75 000/ml initially). There was no history of taking quinine in the previous 7 days.

A second iv canula was inserted in the opposite arm for repeated bloodsampling in heparinized tubes. The healthy subjects were sampled at 0, 0.5, 1, 2, 4, 8, 24, 30 and 48 h after starting the quinine infusion; the patients 12 times during the first 24 h (at 0, 1, 2, 4, 6, 8, 12, 14, 16, 20, 22 and 24 h) and 8 times thereafter, i.e. before and after one of the mid-infusions and before and after the last (9th) infusion up till 100 h (at 64, 68, 72, 76, 84, 92 and 100 h). All blood samples were immediately centrifuged and stored at -20°C until analysis. Parasitemia was assessed every 12 h by thin and thick capillary bloodfilms.

Plasma quinine concentrations were measured by HPLC as described previously by Edstein et al. [3]. Day to day reproducibility showed a coefficient of variation of 8%. Elimination half-life ($t_{1/2}$), apparent volume of distribution (V_D), and total clearance (CL) were calculated according to standard procedures, assuming first order kinetics in a one compartment model. Area under the curve (AUC) was estimated using the trapezoid rule and extrapolating the elimination curve to infinity. (1-Acid glycoprotein (ÓGP), the main plasma binding protein for quinine, was measured daily on the first four consecutive days in the patients and once in the healthy subjects. Data were related to mathematical models by the NONLIN computer program.

The hearing function during the treatment with quinine was studied with conventional audiometry (CA) at 250, 500, 1000, 2000, 4000, 8000 Hz and with high frequency audiometry (HFA) at 10, 12, 14 and 16 kHz. Pure tone thresholds from 250–8000 Hz were determined with an Interacoustics AC 4 audiometer and TDH-39 headphones. For measuring pure tone thresholds from 10–16 kHz a (Demlar 20 HF) audiometer and dynamic earphones with a ceramic diaphragm (koss HV/IA) were used. Detectable perceptive hearing loss was defined as >20 dB at one or 15 dB at more than one frequency. Audiometry was performed before treatment; the healthy subjects were examined subsequently between 2–3.5 h, 25–31 h and 7–9 days (three subjects) after the start of the quinine infusion; patients were tested again on day 3, on day 4 or 5, and between day 10 and 15. Prodromal signs of ototoxicity (tinnitus and dizziness) were assessed by questionnaire.

The protocols for this study were approved by the Medical Ethical Committee of the Academic Medical Centre of Amsterdam and informed consent was obtained.

3. Results

3.1. Quinine pharmacokinetics

The characteristics of the healthy subjects and the patients are summarised in Table 1 and the pharmacokinetic parameters in Table 2. All patients were previously healthy. In the patients the fever lasted 3 ± 2 days (mean $\pm$ S.D.). It took

Table 1
Characteristics of the subjects

	Healthy volunteers	Patients
Number (male/female)	12 (8/4)	10 (6/4)
Age (years)	24 (19–32)	34 (20–49)
Bodyweight (kg)	64 (51–80)	76 (53–88)
Parasitemia (count/mm^3)	NA[a]	14 900 (120–75 000)

Ranges between parentheses.
[a]Not applicable.

36 ± 18 (mean $\pm$ S.D.) h for the parasite count to fall below 10% of the pre-treatment counts. Complete clearance of *P. falciparum* was reached after 63 ± 36 h (mean $\pm$ S.D.).

In the healthy subjects the plasma quinine concentration data (C_Q) fitted reasonably well to the one compartment model. After the 4 h infusion of 300 mg quinine-diHCl the maximum concentration (C_{max}) was 2.0 ± 0.5 mg/l (mean $\pm$ S.D.). The ÓGP concentration in the healthy subjects was about one third of the value found in the patients: 0.58 ± 0.24 g/l. No correlation was found between ÓGP and C_{max}, ÓGP and AUC or bodyweight and V_D.

The patients with *Plasmodium falciparum* malaria received a dose of 8.0 ± 1.4 mg/kg quinine-diHCl as a result of the fixed dose of 600 mg quinine. In most patients the C_Q tended to reach a steady state, in two it continued to increase during the 3 treatment days, whereas in one case it started to drop before the end of the 3 days treatment period. C_Q declined monoexponentially from the end of the last infusion (at 68 h). The V_D in the initial phase can be estimated 1.2 ± 0.3 l/kg (dose per kg/C_Q at 4 h), which is less than half the V_D after 3 days. $C_Q > 10$ mg/l were reached at 19 ± 5 h; The mean C_Q (C_{Qmax}) ranged between 8.6 and 18.5 mg/l. (C_{Qmax}) appeared to be positively correlated with bodyweight ($r = 0.72$) instead of inversely, which could not be explained. The concentration of ÓGP did not change significantly during the first 4 days and averaged to 1.83 ± 0.36 g/l. In malaria patients the AUC was related to the mean concentration of ÓGP ($r = 0.85$, $P = 0.01$, $n = 10$) and C_{Qmax} to the concentration of ÓGP on the same day ($r = 0.89$, $P < 0.01$, $n = 7$).

In the healthy subjects such a comparable association was not found. In that group no association was found between bodyweight and V_D, even when corrected for ÓGP.

Table 2
Pharmacokinetic parameters in healthy subjects and in patients, calculated on basis of the elimination phase data

	Mean (S.D.)	
	Healthy subjects	Patients
$t_{1/2}$ (h)	9.7 (2.8)	19.9 (9.6)
V_d (l/kg)	2.0 (0.5)	2.7 (1.5)
CL (ml/kg and min)	2.6 (0.9)	1.6 (0.7)
C_{Qmax} (mg/l)		13.0 (2.8)
t_{max} (h)		48 (16) (measured) 99 (48) (calculated)
$t_{Cmax,87.5\%}$		30 (17) (measured) 60 (29) (calculated)
$t_{c \geq 10\ mg/l}$		19 (5)

$t_{1/2}$, elimination half-life.
V_d, apparent volume of distribution.
CL, total clearance.
C_{Qmax}, maximal plasma quinine concentration.
t_{max}, time to C_{Qmax}.
$t_{Cmax,87.5\%}$, time to 87.5% of C_{Qmax}.
$t_{c \geq 10\ mg/l}$, time to a plasma quinine concentration of 10 mg/l.

3.2. Audiological data

In the healthy persons no subjective signs of ototoxicity were registered. All pre-treatment audiograms were normal. During the infusion (between 2–3.5 h) there was unilateral hearing loss in 5 subjects, 4 times in HFA, once in CA. Maximal hearing loss was measured 2–4 h after the infusion unilaterally in 9 subjects, 7 times in HFA and twice in CA. Hearing losses did not exceed 25 dB except in one ear, which showed 35 dB loss at 10 and 13 kHz with a persistent loss of 20 dB at 14 kHz after 4 months. All others recovered completely after 24 h or 1 week (one ear). The findings are summarised in Table 3.

Table 3
Audiometric findings in healthy subjects

Hearing loss (dB)	Number of hours after start of infusion					
	2–3.5		6–8		25–31	
	CA	HFA	CA	HFA	CA	HFA
No loss	20	11	16	7	23	14
$\geq 2 \times 10$ or 1×15	3	9	7	11	1	8
$\geq 2 \times 15$ or 1×20	1	2	1	2		2
$\geq 2 \times 20$ or 1×25		2		3		
$\geq 2 \times 25$ or 1×30						
$\geq 2 \times 30$ or 1×35						
$\geq 2 \times 35$ or 1×40				1		

Number of ears (12 patients, 24 ears).
CA, standard frequencies (250, 500, 1000, 2000, 4000 and 8000 Hz).
HFA, high frequencies (10, 12, 14 and 16 kHz).

All patients with the *Plasmodium falciparum* infection experienced adverse effects related to ototoxicity: 9 had impaired hearing, 11 tinnitus, 8 had a feeling of pressure on the ears and 4 felt giddiness. The audiograms of 9 patients were suitable for analysis. In 7 patients the final audiogram was used as a reference, because it appeared to be better than the pre-treatment one. The final audiograms were all within normal limits, but because of the limited value of the pre-treatment audiogram small persistent hearing losses as were suggested in one healthy subject could not be excluded. No hearing loss was measurable in the other 2 patients 1 week after the infusion was stopped. The hearing loss was maximal on the third day of quinine infusion (see Table 4) and comparable in standard and high frequencies. Recovery tended to be slower in HFA.

4. Discussion

Changes in the hearing function after quinine administration were studied in healthy Caucasian volunteered subjects and patients suffering from falciparum malaria disease. Quinine-dihydrochloride was administered intravenously as a single dose of 300 mg to 12 healthy subjects and as multiple doses of 600 mg in 4 h every 8 h in 10 *Plasmodium falciparum* malaria patients. Our pharmacokinetical data in the white healthy persons indicate no association between body weight and V_d even when corrected for ÓGP. In the malaria patients there was a poor correlation between bodyweight and quinine plasma concentrations. Changes in quinine pharmacokinetic parameters over time were confirmed. Both in healthy persons and in malaria patients considerable but reversible hearing losses were detected.

Ototoxic reactions due to quinine are well-known. Permanent deafness after quinine administration is rare. In animal experiments inner ear changes have demonstrated following toxic levels of quinine administered for long periods [4]. Ultrastructural changes in the cochlea have been seen in the outer hair cells of the guinea pig after exposure to quinine [5]. On the other hand Rybak and Whitworth showed that quinine can reduce the toxicity of loop diuretics [6]. Reversible hearing impairment related to the quinine blood concentrations was demonstrated in guinea pigs by Alván et al. [7]. At the moment the mechanism of quinine ototoxicity seems to be multifactorial. The anatomical studies suggest no permanent cochlear damage due to quinine [8].

Nielsen-Abbring et al. demonstrated that ototoxicity occurs when plasma quinine concentrations exceed 5 mg/l and that the high frequency hearing selectively are affected [9]. Studies on the ototoxicity of quinine in humans are scarce how-

Table 4
Audiometric findings in patients

Hearing loss (dB)	9 patients/18 ears			
	3rd day of infusion		1st or 2nd day after infusion	
	CA	HFA	CA	HFA
No loss		1	7	7
$\geq 2 \times 10$ or 1×15[a]		1	3	2
$\geq 2 \times 15$ or 1×20	2	1	7	4
$\geq 2 \times 20$ or 1×25	3		1	3
$\geq 2 \times 25$ or 1×30	2	4		1
$\geq 2 \times 30$ or 1×35	4	6		1
$\geq 2 \times 35$ or 1×40	5	1		
$\geq 2 \times 40$ or 1×45				
$\geq 2 \times 45$ or >45	2	4		

CA, standard frequencies (250, 500, 1000, 2000, 4000 and 8000 Hz).
HFA, high frequencies (10, 12, 14 and 16 kHz).
[a] i.e. 10 dB at ≥ 2 measured frequencies or 15 dB at one frequency.

ever and there is still some questions about the reversibility of the quinine induced hearing loss [10,11]. This study is one of the first in which the ototoxicity of quinine are investigated in healthy persons and patients with malaria. Severe hearing loss was noted especial in the high frequencies in 9 of the 12 healthy subjects. Despite the low dose of 300 mg quinine over 4 h in this group, the blood concentration is probably comparable with 6 mg/l in malaria patients, because the concentration of α1-Acid glyoprotein (the main plasma binding protein for quinine) in volunteers was only one third of the value in patients. One ear showed a persistent hearing loss at 14 kHz of 20 dB, but it was only a single observation. Hearing losses tended to occur selectively in the HFA in the healthy subjects. This could not be demonstrated in the malaria patients; recovery however tended to be prolonged in the HFA. This phenomena has been described before in a case report [9]. Since in 7 of 9 evaluable patients the final audiogram was better than the pre-treatment one, the value of the latter is limited and small persistent hearing losses due to quinine cannot be excluded. Nevertheless quinine induced ototoxicity in patients and volunteers appears to be largely, if not completely, reversible.

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