The pharmacokinetics of chloroquine in healthy Thai subjects and patients with *Plasmodium vivax* malaria

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The pharmacokinetics of chloroquine (CQ) and desethylchloroquine (DECQ) were studied in seven male Thai patients with *P. vivax* malaria and seven healthy male Thais, after the standard oral dosage regimen of CQ (a total dose of 1500 mg given over 3 days). All patients showed a rapid initial response to the treatment with median (range) values of fever and parasite clearance times of 13.7 (2–47) and 58 (33–38) h, respectively. In the patients, the median range Cmax value was significantly higher (1547 (996–2446) vs 838 (656–1587) ng ml⁻¹), and AUC(0,28d) was greater (281 (250–515) vs 122 (103–182) µg ml⁻¹ h⁻¹). In addition, the median (AUC(0,28d) of DECQ was significantly greater (170 (72–265) vs 77 (49–140) µg ml⁻¹ h⁻¹). The AUC(0,28d) ratio of DECQ to CQ in patients was significantly higher than that in healthy subjects (0.67 (0.43–0.90) vs 0.51 (0.29–0.61)).

**Keywords** chloroquine malaria pharmacokinetics

**Introduction**

Chloroquine (CQ) is the treatment of choice for vivax malaria. However, in the past 5 years there have been increasing reports of recurrence of *P. vivax* parasitaemia after therapeutic or prophylactic regimens of CQ in some parts of the world [1–7]. In Thailand, in spite of the total loss of efficacy of chloroquine in the treatment of *P. falciparum* malaria, the efficacy of the drug against *P. vivax* malaria has been complete [8–9], although declining susceptibility of the parasite to CQ was observed in vitro (Tan-ariya *et al.*, 1994, submitted for publication). The pharmacokinetics of CQ and its major plasma metabolite desethylchloroquine (DECQ) were compared in male Thai subjects with *P. vivax* malaria and healthy subjects, in order to define any differences which might account for altered response in patients.

**Methods**

Seven healthy male Thai subjects, and seven male Thai patients with *P. vivax* malaria, aged between 18 and 35 years and weighing 45 to 68 kg, were recruited for the study. Written informed consent for participation was obtained from each volunteer. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

The healthy subjects were non-smokers, non-drinkers and had no previous history of liver or kidney diseases. None was on regular medication and no other drugs were taken during the study. They were admitted to the Bangkok Hospital for Tropical Diseases on the first day of drug administration and returned for blood sampling daily until day 14, and again on days 21 and 28. The patients were admitted to the Bangkok Hospital for Tropical Diseases for 28 days. It was not possible to keep the subjects in the hospital for longer than this time.

On admission, each subject had a physical examination, evaluation of vital signs, a 12-lead electrocardiogram, routine blood examinations (haematology, serum biochemistry), and urinalysis. Venous blood samples (2 ml) were drawn for measurement of baseline whole blood CQ and DECQ concentrations.

All subjects received CQ (Chloroquine phosphate, Government Pharmaceutical Organization of Thailand; 1 tablet of 250 mg salt contains 150 mg base) in a total dose of 1500 mg over 3 days (600 mg initially,
followed by 300 mg at hours 6, 24 and 48). In healthy subjects, the drug was administered following
an overnight fast and the subjects were allowed to
take food 2 h after drug administration.

Following the first dose of CQ, a total of 18 blood
samples (2 ml each) were collected at 6, 12, 24, and
48 h, daily until day 14, and on days 21 and 28. At 6,
24 and 48 h, blood samples were collected prior to
the dose of CQ. Whole blood samples were collected
into lithium-heparinized plastic tubes and stored at
−70°C until analysis.

Adverse effects occurring after drug administration
were monitored by daily questionnaires and physical
examination for 7 days. Complete blood count, uri-
alysis and blood biochemistry investigations were
performed on days 2, 4, 7 and then weekly until day
28. An electrocardiogram was recorded daily for 7
days then weekly for the remainder of the follow-up
period.

In patients, a parasite count was performed every
6 h after the treatment until parasitaemia fell below
the level of microscopic detection in a thick smear,
then twice daily until day 28. Before discharge, an
antirelapse drug primaquine phosphate (15 mg, o.d.
Government Pharmaceutical Organization of Thai-
land), was given for 14 days to all patients.

CQ and DECQ concentrations in whole blood were
measured by h.p.l.c. using the method of Alvan et
al. [10] with modifications. In brief, whole blood
samples containing 1000 ng primaquine as an internal
standard were added to 1 ml of 0.1 m sodium hy-
droxide. After vortexing for 30 s, the mixture was
extracted with 6 ml dichloromethane by mechanical
tumbling for 30 min. The organic phase was sepa-
rated by centrifugation (at 1000 g, 10 min, 4°C), and
evaporated to dryness under a stream of nitrogen gas
at 37°C. The residue was redissolved in the mobile
phase (50 μl) and 20 μl was injected onto a reversed-
phase C18 column (Techopak-10 C18, 10 μm particles,
25 cm × 4.6 mm i.d., h.p.l.c. Technology, UK). The
mobile phase consisted of acetonitrile and phosphate
buffer pH 2.95 (25:75 v/v) containing perchlorate
(200 mmol l⁻¹). The flow rate was 2.8 ml min⁻¹ with
u.v. detection at 254 nm. The limit of determination
was 5 ng ml⁻¹ for CQ and 10 ng ml⁻¹ for DECQ. The
intra- and inter-assay coefficients of variation were,
respectively, 7.5% and 9.1% at 50 ng ml⁻¹, 5.9% and
1% at 500 ng ml⁻¹ and 7.8% and 6.1% at 1000 ng ml⁻¹
for CQ. The corresponding values for DECQ were
5.2% and 4.2% at 50 ng ml⁻¹, 2% and 1% at 500 ng
ml⁻¹ and 9.2% and 1.4% at 1000 ng ml⁻¹.

The maximum blood drug concentration (Cmax) was
declared as the highest concentration observed during
the sampling time. An apparent elimination rate con-
stant (λb,28d) was estimated by least squares regres-
sion analysis of at least 4 concentrations from day
8 onwards, and the corresponding half-life (t1/2,28d)
from the ratio of 0.693/λb,28d. The values of AUC(0,28d)
were calculated using the linear trapezoidal rule.

The pharmacokinetic parameters of CQ or DECQ
in healthy subjects and patients were analysed using
the Mann-Whitney U test.

Results
The healthy subjects and patients were matched for
age (median 28, range 27–35 vs median 21, range
18–41 years) and weight (median 59, range 55–68 vs
median 54, range 45–65 kg). None of the healthy
subjects had signs or symptoms of malaria para-
sitaemia in peripheral blood smears on admission.
Median and range admission parasitaemia in patients
was 757 (138–11480) μl⁻¹. The adverse effects of CQ
in both groups of subjects were mild and self-limit-
ing; one of the patients and two healthy subjects
complained of dizziness. All except one patient com-
plained of headache, five patients and one healthy
subject had nausea and abdominal distress, but no
vomiting. There were no noticeable drug-related
haematological effects, biochemical or ECG changes
during the course of follow-up.

All patients showed a rapid initial response to the
treatment with median (range) values of fever clear-
ance time (the time taken for the temperature to
return to below 37.3°C and remain at that value for
at least 24 h) and parasite clearance time (the time
taken for the parasite count to fall below the level
of microscopic detection) of 13.7 (2–47) and 58 (33–
28) d.

Figure 1 Median plots of whole blood concentrations
of CQ (●) and DECQ (○) in a) healthy subjects and
b) patients with P. vivax malaria.
Discussion

Blood concentrations of both CQ and DECQ observed in the study were similar to those reported by others [11]. After multiple oral doses of CQ in both malaria patients and healthy subjects, systemic exposure of CQ was always higher than that of DECQ. The higher $C_{\text{max}}$ and AUC values observed in the

Table 1  Pharmacokinetic parameters (median and range) of CQ and DECQ derived from data collected over 28 days in seven healthy Thai male subjects and seven patients after administration of 1500 mg chloroquine over 3 days

<table>
<thead>
<tr>
<th>Healthy subjects</th>
<th>CQ</th>
<th>DECQ</th>
<th>Patients (P. vivax malaria)</th>
<th>CQ</th>
<th>DECQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng ml$^{-1}$)</td>
<td>838 (656-1587)$^a$</td>
<td>428 (159-637)</td>
<td>1547 (996-2446)</td>
<td>591 (253-761)</td>
<td></td>
</tr>
<tr>
<td>AUC(0,28d) (μg ml$^{-1}$ h)</td>
<td>122 (103-182)$^b$</td>
<td>77 (49-140)$^c$</td>
<td>281 (250-515)</td>
<td>170 (72-265)</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{½}}$ (h)</td>
<td>150 (103-266)</td>
<td>198 (152-329)</td>
<td>201 (155-224)</td>
<td>205 (190-276)</td>
<td></td>
</tr>
</tbody>
</table>

Significantly different from values in patients: (a) $P = 0.039$ (95% CI -234-1124); (b) $P = 0.002$ (95% CI 127-291); (c) $P = 0.013$ (95% CI 5.125).

References


(Received 1 October 1993, accepted 31 May 1994)