CASE REPORT

QUININE TOXICITY WHEN GIVEN WITH DOXYCYCLINE AND MEFLOQUINE

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Abstract. The pharmacokinetic and dynamic interactions among 3 antimalarials, *ie* quinine, doxycycline and mefloquine was observed in a 26 year-old Thai male patient with falciparum malaria. During the acute episode of the infection, the patient was treated with an intravenous dose of quinine hydrochloride at 600 mg qid, together with an oral dose of doxycycline 100 mg bid. Due to severe nausea, tinnitus and the persistence of parasitemia in peripheral blood smears, the dose of quinine was reduced 2 days after the first treatment to 300 mg; concurrently oral mefloquine 750 mg was given as 2 divided doses at 24 hours apart. During the course of treatment, the patient developed hearing loss; deafness of the right ear lasted for one week after stopping quinine administration. Higher plasma quinine and lower whole blood mefloquine concentrations than would be expected from the simulation profiles were detected 4 days after the first treatment. However, the concentration of mefloquine was increased upon the cessation of quinine treatment.

Quinine is the chief alkaloid of the bark of the Cinchona tree. It has been used extensively as an antimalarial over a long period. During the late 1940s, the antimalarial chloroquine was shown to be more effective and less toxic, so the use of quinine declined considerably. However, the emergence of chloroquine resistance occurred approximately 10 years after its initial use. This was followed by the introduction of sulfadoxine-pyrimethamine for the treatment of uncomplicated chloroquine resistant falciparum malaria, but in due course, drug resistance and toxicity (Miller *et al,* 1986; Philips-Howard and West, 1990) of sulfadoxine-pyrimethamine have limited its clinical use. Mefloquine was introduced as a simple single dose therapy for multidrug resistant falciparum malaria in recent years. However, emergence of mefloquine resistance has been reported in the past 2 years in certain areas of Southeast Asia (Bunnag *et al,* 1992; Karbwang *et al,* 1992; 1993; Na Bangchang *et al,* 1993). This was compounded by neuropsychiatric toxicity of mefloquine (Rouveix *et al,* 1989; Weinke *et al,* 1992) which was estimated to occur in one in 215 therapeutic users (Weinke *et al,* 1991). Quinine gained popularity for uncomplicated multidrug resistant malaria and it is the drug of choice for severe falciparum malaria despite declining efficacy. In uncomplicated multiple drug resistant falci-

parum malaria, the cure rate has decreased to 75% when using quinine alone (Karbwang and Harinasuta, 1992). The cure rate can be imporved when quinine is combined with tetracycline 1 g/day; the course of treatment needs to be 7 days to achieve a satisfactory cure rate. Nevertheless, cinchonism, which is commonly seen with quinine treatment, limits the completion of the treatment course. In most cases, patients develop tinnitus 2-3 days after starting treatment and would stop taking quinine as a consequence of this side-effect. The patients would then seek another treatment from the malaria clinic of government hospital. The first line drug treatment for falciparum malaria in Thailand is mefloquine. The use of this combination or one after another within a short interval (*ie* within hours) may result in severe drug interactions, as quinine and mefloquine have similar chemical structures (Fig 1). We describe the pharmacokinetic interaction of quinine-doxycycline-mefloquine and the side-effects in a patient with uncomplicated falciparum malaria.

A 26 year-old male patient with falciparum malaria was admitted to a Provincial Hospital in the Southern part of Thailand. He had no previous treatment with antimalarials prior to the hospitalization. He was immediately treated with quinine
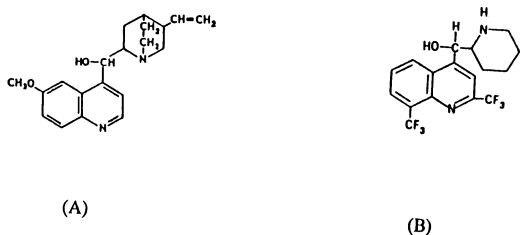
(A)

(B)

Fig 1—Chemical structures of (A) quinine and (B) mefloquine.

hydrochloride 600 mg, intravenously every 8 hours, together with doxycycline 100 mg, orally every 12 hours. After 2 days of treatment, the dose of quinine was reduced to 300 mg every 6 hours, due to severe nausea and tinnitus. During this time, falciparum malaria parasites were still detectable in the peripheral blood smear. The doctor in charge decided to add mefloquine as the thrid antimalarial drug to the treatment regimen. Mefloquine was given orally, 500 mg as the first dose, followed by another 250 mg 24 hours later (Fig 2). During treatment, the patient developed loss of hearing. The ability to hear was partially lost in the left ear and totally lost in the right ear. The patient was then transferred to the Bangkok Hospital for Tropical Diseases. When seen, the patient was febrile with flushed face, both palms were reddish, the temperature was 38°C, the pulse rate and blood pressure were 84/minute and 120/70 mmHg, respectively. The patient had severe headache, nausea and vomiting, severe tinnitus in the left ear and he was not able to hear at all with the right ear. The patient was not jaundiced but his liver SGPT was increased 4-fold. No sign of kidney failure was noted. No malaria parasite was seen in his peripheral blood smear and therefore specific treatment for malaria was not given. The patient gradually improved; fever, nausea, vomiting and tinnitus disappeared 2-3 days after admission but deafness of the right ear lasted for one week after stopping quinine administration. On follow-up at 28 days after mefloquine treatment, no malaria was detected in his peripheral blood.

The plasma quinine and whole blood mefloquine concentrations were measured daily during hospitalization at the Bangkok Hospital for Tropical Diseases; the plasma concentration profiles are shown in Fig 2. It should be noted that the concentration of quinine obtained in this patient was higher than expected from the simulation concen-
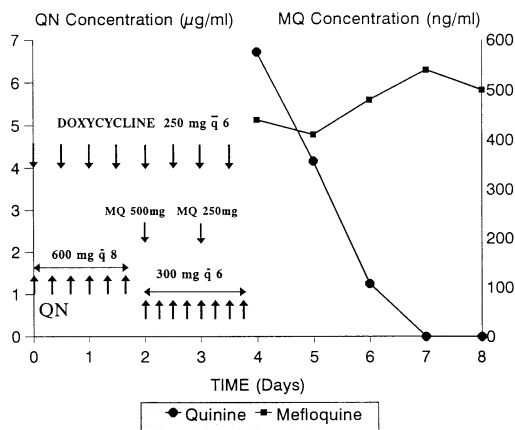

Fig 2—Plasma quinine and whole blood mefloquine concentrations during the treatment with quinine, doxycycline and mefloquine.

tration-time curve of the same dosage regimen (Fig 3). The quinine concentration at the time of admission to the Bangkok Hospital for Tropical Diseases (ie 48 hours after the last dose of quinine) was 6 μg/ml; this should have been less than 1 μg/ml if quinine was used alone.

The mefloquine concentration was lower than expected from simulation concentration-time curve of the same regimen and increased upon the cessation of quinine concentration (Fig 2).

Emergence of multiple drug resistant falciparum malaria has prompted an increased use of quinine in the treatment of malaria. Quinine has a rapid action against asexual forms of falciparum

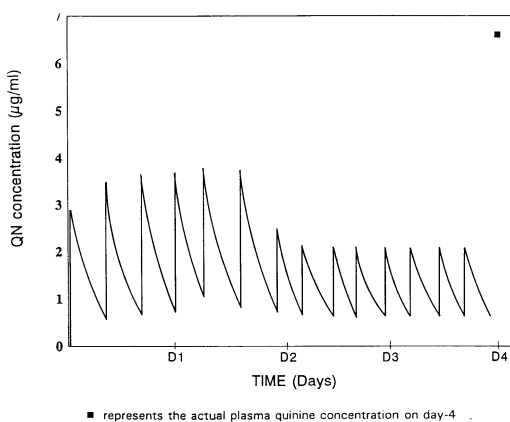■ represents the actual plasma quinine concentration on day-4 .

Fig 3—Simulation curve of quinine.

malaria, however decreasing sensitivity to quinine has been reported in Southeast Asia, where it has been used extensively unsupervised (Chongsuphajaisiddhi *et al,* 1981; Suebsaeng *et al,* 1986; Karbwang and Harinasuta, 1992). The quinine concentration requirement for falciparum malaria curative treatment is higher.

Cinchonism is a common side-effect of quinine at the therapeutic concentrations. It is characterized by tinnitus, headache, disturbed vision and occasionally deafness. Quinine induced deafness is reversible. Hearing impairment and tinnitus are always experienced when plasma quinine concentrations exceed 5 µg/ml (15 µmol/l); concentrations below 1.6 µg/ml (5 µmol/l) are not associated with any subjective hearing symptoms (Alvan *et al,* 1991). Quinine causes an initial generalized stimulation of the central nervous system leading to fever, delirium and increased ventilatory rate, which may be followed by coma and respiratory depression. Quinine may cause myocardial depression, prolongation of QTc interval and peripheral vasodilatation. Despite narrow therapeutic range and numerous side-effects, quinine remains one of the few effective antimalarials for the treatment of multiple drug resistant falciparum malaria (WHO, 1990).

The concentrations of quinine obtained from this patient were higher than expected from the simulation concentration-time curve (Fig 3), suggesting that there was an interaction between quinine and doxycycline. Tetracycline has been shown to increase the concentration of quinine when given concurrently (Karbwang *et al,* 1991). This is one of the explanations for a better cure rate when compared to quinine alone in quinine resistant falciparum malaria where higher quinine concentration is required (Chongsuphajaisiddhi *et al,* 1981). The interaction of quinine and doxycycline was further compounded by the administration of mefloquine. In spite of low quinine concentration (Fig 2), deafness in this patient persisted for 7 days after discontinuation of quinine treatment. Hearing loss seems to be augmented in the presence of mefloquine as at this concentration, deafness is rarely seen. The quinine concentration of this patient on the second day after admission was only 4 µg/ml, but the patient still had total hearing loss in his right ear. In malaria patients, hearing loss is pronounced during quinine treatment, the loss is marked during parenteral administration and this symptom usually disappears

after stopping quinine treatment (Karlsson *et al,* 1990). Drug interaction between quinine and mefloquine is likely. Mefloquine is highly plasma protein binding and might have competed with quinine for protein binding sites. This may result in a higher free quinine concentration and as a consequence, greater adverse effects (cinchonism and loss of hearing) due to the quinine. It is unfortunate that the unbound quinine was not measured to support this assumption. Interaction of mefloquine with halofantrine has been reported in a recent study; the enhancement of the lengthening of QTc interval by halofantrine in falciparum malaria patients who had previous mefloquine treatment was observed (ter Kuile *et al,* 1993); however, the mechanism is not known.

The increase in mefloquine concentration after the cessation of quinine administration had also been seen in a previous study (Chantavanich *et al,* 1985). This may be explained by the vacancy of protein binding sites after the cessation of quinine, so that mefloquine was retracted from the large tissue pool and occupied these protein binding sites.

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